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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

(57) Abstract: The present invention relates to compositions containing novel proteins and methods of using those compositions for the diagnosis and treatment of immune related diseases.

COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

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Field of the Invention

The present invention relates to compositions and methods useful for the diagnosis and treatment of immune related diseases.

Background of the Invention

10 Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation 15 or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

20 Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

25 Immune related diseases could be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

30 Macrophages represent an ubiquitously distributed population of fixed and circulating mononuclear phagocytes that express a variety of functions including cytokine production, killing of microbes and tumor cells and processing and presentation of antigens. Macrophages originate in the bone marrow from stem cells that give rise to a bipotent granulocyte/macrophage cell population. Distinct granulocyte and macrophage colony forming cell lineages arise from GM-CSF under the influence of specific cytokines. Upon division, monoblasts give rise to promonocytes and monocytes in the bone marrow. From there, monocytes enter the circulation. In response to particular stimuli (e.g. infection or foreign bodies) 35 monocytes migrate into tissues and organs where they differentiate into macrophages.

Macrophages in various tissues vary in their morphology and function and have been assigned different names, e.g. Kupffer cells in the liver, pulmonary and alveolar macrophages in the lung and microglial cells in the central nervous system. However, the relationship between blood monocytes and tissue macrophages remains unclear.

In the present study monocytes were differentiated into macrophages by adherence to plastic in the presence of a combination of human and bovine serum. After 7 days in culture, monocytes-derived macrophages display features typical of differentiated tissue macrophages including their ability to phagocytose opsonized particles, secretion of TNF-alpha upon lipopolysaccharide (LPS) stimulation, 5 formation of processes and the presence of macrophage cell surface markers.

Using microarray technologies, gene transcripts from non-differentiated monocytes harvested before adhering were compared with those at 1 day and 7 days in culture. Genes selectively expressed in monocytes or macrophages could be used for the diagnosis and treatment of various chronic inflammatory or autoimmune diseases in the human. In particular, surface expressed molecules or transmembrane receptors 10 involved in monocyte/macrophage adhesion and endothelial cell transmigration could provide novel targets to treat chronic inflammation by interference with the homing of these cells to the site of inflammation. In addition, transmembrane inhibitory receptors could be used to down-regulate monocyte/macrophage effector functions. Therapeutic molecules can be antibodies, peptides, fusion proteins or small molecules.

Despite the above research in monocyte/macrophages, there is a great need for additional 15 diagnostic and therapeutic agents capable of detecting the presence of monocyte/macrophage mediated disorders in a mammal and for effectively reducing these disorders. Accordingly, it is an objective of the present invention to identify polypeptides that are differentially expressed in macrophages as compared to non-differentiated monocytes, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of 20 monocyte/macrophage mediated disorders in mammals.

Summary of the Invention

A. Embodiments

The present invention concerns compositions and methods useful for the diagnosis and treatment of 25 immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which are a result of stimulation of the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of 30 the immune response would be beneficial. Alternatively, molecules that suppress the immune response attenuate or reduce the immune response to an antigen (e.g., neutralizing antibodies) can be used therapeutically where attenuation of the immune response would be beneficial (e.g., inflammation). Accordingly, the PRO polypeptides, agonists and antagonists thereof are also useful to prepare medicines and medicaments for the treatment of immune-related and inflammatory diseases. In a specific aspect, such 35 medicines and medicaments comprise a therapeutically effective amount of a PRO polypeptide, agonist or antagonist thereof with a pharmaceutically acceptable carrier. Preferably, the admixture is sterile.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprises contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a

native sequence PRO polypeptide. In a specific aspect, the PRO agonist or antagonist is an anti-PRO antibody.

In another embodiment, the invention concerns a composition of matter comprising a PRO polypeptide or an agonist or antagonist antibody which binds the polypeptide in admixture with a carrier or 5 excipient. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide or antibody. In another aspect, when the composition comprises an immune stimulating molecule, the composition is useful for: (a) increasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) stimulating or enhancing an immune response in a mammal in need thereof, (c) increasing the proliferation of monocytes/macrophages in a mammal in need thereof in response to an antigen, (d) 10 stimulating the activity of monocytes/macrophages or (e) increasing the vascular permeability. In a further aspect, when the composition comprises an immune inhibiting molecule, the composition is useful for: (a) decreasing infiltration of inflammatory cells into a tissue of a mammal in need thereof, (b) inhibiting or reducing an immune response in a mammal in need thereof, (c) decreasing the activity of monocytes/macrophages or (d) decreasing the proliferation of monocytes/macrophages in a mammal in need 15 thereof in response to an antigen. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In another embodiment, the invention concerns a method of treating an immune related disorder in a mammal in need thereof, comprising administering to the mammal an effective amount of a PRO 20 polypeptide, an agonist thereof, or an antagonist thereto. In a preferred aspect, the immune related disorder is selected from the group consisting of: systemic lupus erythematosis, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis, idiopathic inflammatory myopathies, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, demyelinating diseases of 25 the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious, autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin 30 diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease.

In another embodiment, the invention provides an antibody which specifically binds to any of the 35 above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which 40 preferably has nonhuman complementarity determining region (CDR) residues and human framework region

(FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic antibody.

In yet another embodiment, the present invention provides a composition comprising an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. Preferably, the composition is sterile. The composition may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Alternatively, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

10 In a further embodiment, the invention concerns an article of manufacture, comprising:
(a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
(b) a container containing said composition; and
(c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of an immune related disease. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

15 In yet another embodiment, the present invention concerns a method of diagnosing an immune related disease in a mammal, comprising detecting the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample indicates the presence of immune related disease in the mammal from which the test tissue cells were obtained.

20 In another embodiment, the present invention concerns a method of diagnosing an immune disease in a mammal, comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and a PRO polypeptide, in the test sample; wherein the formation of said complex is indicative of the presence or absence of said disease. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence or absence 25 of an immune disease in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected of having a deficiency or abnormality of the immune system.

30 In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a test sample of cells suspected of containing the PRO polypeptide to an anti-PRO antibody and determining the binding of said antibody to said cell sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

35 In another embodiment, the present invention concerns an immune-related disease diagnostic kit, comprising an anti-PRO antibody and a carrier in suitable packaging. The kit preferably contains

instructions for using the antibody to detect the presence of the PRO polypeptide. Preferably the carrier is pharmaceutically acceptable.

In another embodiment, the present invention concerns a diagnostic kit, containing an anti-PRO antibody in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO polypeptide.

In another embodiment, the invention provides a method of diagnosing an immune-related disease in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of the PRO polypeptide in said test sample is indicative of the presence of an immune-related disease in said mammal.

10 In another embodiment, the present invention concerns a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

15 (b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the invention concerns a method for identifying a compound capable of inhibiting the activity of a PRO polypeptide comprising contacting a candidate compound with a PRO polypeptide under conditions and for a time sufficient to allow these two components to interact and 20 determining whether the activity of the PRO polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

25 (b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally express the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO 30 polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In yet another embodiment, the present invention concerns a method for treating an immune-related disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the nucleic acid is administered via *ex vivo* gene therapy. In a further preferred embodiment, the nucleic acid is comprised 40 within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral or retroviral vector.

In yet another aspect, the invention provides a recombinant viral particle comprising a viral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the viral vector is in association with viral structural proteins.

5 Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention concerns an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular 10 secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles.

In a still further embodiment, the invention provides a method of increasing the activity of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of 15 monocytes/macrophages in the mammal is increased.

In a still further embodiment, the invention provides a method of decreasing the activity of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the activity of monocytes/macrophages in the mammal is decreased.

20 In a still further embodiment, the invention provides a method of increasing the proliferation of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of monocytes/macrophages in the mammal is increased.

25 In a still further embodiment, the invention provides a method of decreasing the proliferation of monocytes/macrophages in a mammal comprising administering to said mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein the proliferation of monocytes/macrophages in the mammal is decreased.

B. Additional Embodiments

In other embodiments of the present invention, the invention provides vectors comprising DNA 30 encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

35 In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

5 In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

10 In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

15 In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an

extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700

nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a 5 routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise 10 a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences herein above identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 15 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, 20 alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 25 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

30 In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 35 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 40 96% amino acid sequence identity.

sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs as disclosed herein.

5 In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as herein before described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

10 Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

15 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

20 In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

25 In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as herein before described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

30 BRIEF DESCRIPTION OF THE DRAWINGS

In the list of figures for the present application, specific cDNA sequences which are differentially expressed in differentiated macrophages as compared to normal undifferentiated monocytes are individually identified with a specific alphanumerical designation. These cDNA sequences are differentially expressed in monocytes that are specifically treated as described in Example 1 below. If 35 start and/or stop codons have been identified in a cDNA sequence shown in the attached figures, they are shown in bold and underlined font, and the encoded polypeptide is shown in the next consecutive figure.

The Figures 1-2517 show the nucleic acids of the invention and their encoded PRO polypeptides. Also included, for convenience is a List of Figures attached hereto as Appendix A, which gives the figure number and the corresponding DNA or PRO number.

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 Figure 3: DNA304680, HSPCB, 200064_at
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 Figure 9: DNA83128, NP_002979.1, 32128_at
 Figure 10: PRO2601
 Figure 11: DNA272223, NP_004444.1, 33494_at
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 Figure 13: DNA327522, NP_000396.1, 33646_g_at
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 Figure 27: DNA304703, NP_005923.1, 36830_at
 Figure 28: PRO71129
 Figure 29: DNA328353, AAB72234.1, 37079_at
 Figure 30: PRO84214
 Figure 31: DNA103289, NP_006229.1, 37152_at
 Figure 32: PRO4619
 Figure 33A-B: DNA255096, NP_055449.1, 37384_at
 Figure 34: PRO50180
 Figure 35: DNA256295, NP_002310.1, 37796_at
 Figure 36: PRO51339
 Figure 37: DNA328354, PARVB, 37965_at
 Figure 38: PRO84215
 Figure 39: DNA53531, NP_001936.1, 38037_at
 Figure 40: PRO131
 Figure 41: DNA254127, NP_008925.1, 38241_at
 Figure 42: PRO49242
 Figure 43: DNA328355, NP_006471.2, 38290_at
 Figure 44: PRO84216
 Figure 45: DNA328356, BC013566, 39248_at
 Figure 46: PRO38028
 Figure 47: DNA328357, 1452321.2, 39582_at
 Figure 48: PRO84217
 Figure 49A-B: DNA328358, STK10, 40420_at
 Figure 50: PRO84218
 Figure 51A-B: DNA328359, BAA21572.1, 41386_i_at
 Figure 52: PRO84219
 Figure 53A-D: DNA328360, NP_055061.1, 41660_at
 Figure 54: PRO84220
 Figure 55: DNA327526, BC001698, 45288_at
 Figure 56: PRO83574
 Figure 57A-B: DNA328361, BAA92570.1, 47773_at
 Figure 58: PRO84221
 Figure 59: DNA328362, NP_060312.1, 48106_at
 Figure 60: PRO84222
 Figure 61: DNA328363, DNA328363, 52651_at
 Figure 62: PRO84685
 Figure 63: DNA328364, NP_068577.1, 52940_at
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 Figure 65A-B: DNA327528, BAB3338.1, 55081_at
 Figure 66: PRO83576
 Figure 67: DNA225650, NP_057246.1, 48825_at
 Figure 68: PRO36113
 Figure 69: DNA328365, NP_060541.1, 58780_s_at
 Figure 70: PRO84224
 Figure 71: DNA328366, NP_079233.1, 59375_at
 Figure 72: PRO84225
 Figure 73: DNA328367, NP_079108.2, 60471_at
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 Figure 81: PRO84228
 Figure 82: DNA323806, NP_075385.1, 200644_at
 Figure 83: PRO80555
 Figure 84: DNA327532, GLUL, 200648_s_at
 Figure 85: PRO71134
 Figure 86: DNA227055, NP_002625.1, 200658_s_at
 Figure 87: PRO37518
 Figure 88: DNA325702, NP_001771.1, 200663_at
 Figure 89: PRO283
 Figure 90: DNA83172, NP_003109.1, 200665_s_at
 Figure 91: PRO2120
 Figure 92: DNA328371, NP_004347.1, 200675_at
 Figure 93: PRO4866
 Figure 94A-B: DNA328372, 105551.7, 200685_at
 Figure 95: PRO84229
 Figure 96: DNA324633, BC000478, 200691_s_at
 Figure 97: PRO81277
 Figure 98: DNA324633, NP_004125.2, 200692_s_at
 Figure 99: PRO81277
 Figure 100: DNA88350, NP_000168.1, 200696_s_at
 Figure 101: PRO2758
 Figure 102: DNA328373, AB034747, 200704_at
 Figure 103: PRO84230
 Figure 104: DNA328374, NP_004853.1, 200706_s_at
 Figure 105: PRO84231
 Figure 106: DNA328375, NP_002071.1, 200708_at
 Figure 107: PRO80880

Figure 108: DNA328376, NP_001210.1, 200755_s_at
Figure 109: PRO1015
Figure 110A-B: DNA269826, NP_003195.1, 200758_s_at
Figure 111: PRO58228
Figure 112: DNA325414, NP_001900.1, 200766_at
Figure 113: PRO292
Figure 114A-C: DNA188738, NP_002284.2, 200771_at
Figure 115: PRO25580
Figure 116: DNA328377, NP_003759.1, 200787_s_at
Figure 117: PRO84232
Figure 118: DNA270954, NP_001089.1, 200793_s_at
Figure 119: PRO59285
Figure 120: DNA272928, NP_055579.1, 200794_x_at
Figure 121: PRO61012
Figure 122A-B: DNA327536, BC017197, 200797_s_at
Figure 123: PRO37003
Figure 124: DNA287211, NP_002147.1, 200806_s_at
Figure 125: PRO69492
Figure 126: DNA326655, NP_002803.1, 200820_at
Figure 127: PRO83005
Figure 128A-B: DNA328378, AB032261, 200832_s_at
Figure 129: PRO84233
Figure 130: DNA103558, NP_005736.1, 200837_at
Figure 131: PRO4885
Figure 132: DNA196817, NP_001899.1, 200838_at
Figure 133: PRO3344
Figure 134A-B: DNA327537, NP_004437.1, 200842_s_at
Figure 135: PRO83581
Figure 136: DNA323982, NP_004896.1, 200844_s_at
Figure 137: PRO80709
Figure 138: DNA323876, NP_006612.2, 200850_s_at
Figure 139: PRO80619
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Figure 141: PRO38492
Figure 142: DNA328379, BC015869, 200878_at
Figure 143: PRO84234
Figure 144: DNA325584, NP_002005.1, 200895_s_at
Figure 145: PRO59262
Figure 146A-B: DNA274281, NP_036347.1, 200899_s_at
Figure 147: PRO62204
Figure 148: DNA226028, NP_002346.1, 200900_s_at
Figure 149: PRO36491
Figure 150: DNA326819, NP_000678.1, 200903_s_at
Figure 151: PRO83152
Figure 152: DNA328380, HSHLAEHCM, 200904_at
Figure 153: DNA328381, NP_005507.1, 200905_x_at
Figure 154: PRO84236
Figure 155: DNA272695, NP_001722.1, 200920_s_at
Figure 156: PRO60817
Figure 157: DNA327255, NP_002385.2, 200924_s_at
Figure 158: PRO57298
Figure 159: DNA327540, NP_006818.1, 200929_at
Figure 160: PRO38005
Figure 161: DNA225878, NP_004334.1, 200935_at
Figure 162: PRO36341
Figure 163: DNA328382, 160963.2, 200941_at
Figure 164: PRO84237
Figure 165: DNA328383, NP_004956.3, 200944_s_at
Figure 166: PRO84238
Figure 167A-B: DNA287217, NP_001750.1, 200953_s_at
Figure 168: PRO36766
Figure 169: DNA328384, NP_036380.2, 200961_at
Figure 170: PRO84239
Figure 171: DNA328385, AK001310, 200972_at
Figure 172: PRO730
Figure 173: DNA326040, NP_005715.1, 200973_s_at
Figure 174: PRO730
Figure 175: DNA324110, NP_005908.1, 200978_at
Figure 176: PRO4918
Figure 177: DNA328386, NP_000602.1, 200983_x_at
Figure 178: PRO2697
Figure 179: DNA275408, NP_001596.1, 201000_at
Figure 180: PRO63068
Figure 181: DNA328387, NP_001760.1, 201005_at
Figure 182: PRO4769
Figure 183: DNA103593, NP_000174.1, 201007_at
Figure 184: PRO4917
Figure 185: DNA304713, NP_006463.2, 201008_s_at
Figure 186: PRO71139
Figure 187: DNA328388, BC010273, 201013_s_at
Figure 188: PRO84240
Figure 189: DNA328389, NP_006861.1, 201021_s_at
Figure 190: PRO84241
Figure 191: DNA328390, NP_002291.1, 201030_x_at
Figure 192: PRO82116
Figure 193: DNA196628, NP_005318.1, 201036_s_at
Figure 194: PRO25105
Figure 195: DNA287372, NP_002618.1, 201037_at
Figure 196: PRO69632
Figure 197: DNA328391, NP_004408.1, 201041_s_at
Figure 198: PRO84242
Figure 199: DNA196484, DNA196484, 201042_at
Figure 200: DNA227143, NP_036400.1, 201050_at
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Figure 203: PRO84243
Figure 204: DNA328261, AF130103, 201060_x_at
Figure 205: DNA325001, NP_002794.1, 201068_s_at
Figure 206: PRO81592
Figure 207: DNA328393, NP_001651.1, 201096_s_at
Figure 208: PRO81010
Figure 209: DNA328394, AF131738, 201103_x_at
Figure 210A-B: DNA328395, NP_056198.1, 201104_x_at
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Figure 212: DNA328396, NP_002076.1, 201106_at
Figure 213: PRO84246
Figure 214: DNA328397, NP_002622.1, 201118_at

Figure 215: PRO84247
 Figure 216: DNA328398, NP_002204.1, 201125_s_at
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 Figure 218: DNA325398, NP_004083.2, 201135_at
 Figure 219: PRO81930
 Figure 220: DNA88520, NP_002501.1, 201141_at
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 Figure 222: DNA324480, NP_001544.1, 201163_s_at
 Figure 223: PRO81141
 Figure 224: DNA151802, NP_003661.1, 201169_s_at
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 Figure 226: DNA226662, NP_057043.1, 201175_at
 Figure 227: PRO37125
 Figure 228: DNA88066, NP_002328.1, 201186_at
 Figure 229: PRO2638
 Figure 230: DNA273342, NP_005887.1, 201193_at
 Figure 231: PRO61345
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 Figure 233: PRO84248
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 Figure 243A-B: DNA328402, NP_073713.1,
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 Figure 245: DNA325380, NP_004995.1, 201226_at
 Figure 246: PRO81914
 Figure 247: DNA226615, NP_001668.1, 201242_s_at
 Figure 248: PRO37078
 Figure 249: DNA328403, NP_037462.1, 201243_s_at
 Figure 250: PRO84250
 Figure 251: DNA270950, NP_003182.1, 201263_at
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 Figure 253A-B: DNA328404, NP_003321.1, 201266_at
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 Figure 255: DNA97290, NP_002503.1, 201268_at
 Figure 256: PRO3637
 Figure 257: DNA325028, NP_001619.1, 201272_at
 Figure 258: PRO81617
 Figure 259: DNA328405, NP_112556.1, 201277_s_at
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 Figure 261: DNA328406, NP_001334.1, 201279_s_at
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 Figure 265: DNA328408, NP_060713.1, 201308_s_at
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 Figure 267: DNA325595, NP_001966.1, 201313_at
 Figure 268: PRO38010

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 Figure 270: PRO50165
 Figure 271: DNA150781, NP_001414.1, 201324_at
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 Figure 273: DNA328409, NP_002075.2, 201348_at
 Figure 274: PRO81281
 Figure 275: DNA324475, NP_004172.2, 201387_s_at
 Figure 276: PRO81137
 Figure 277: DNA226353, NP_005769.1, 201395_at
 Figure 278: PRO36816
 Figure 279: DNA328410, NP_004519.1, 201403_s_at
 Figure 280: PRO60174
 Figure 281A-B: DNA328411, 1400253.2, 201408_at
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 Figure 283: DNA328412, NP_060428.1, 201411_s_at
 Figure 284: PRO84257
 Figure 285: DNA273517, NP_000169.1, 201415_at
 Figure 286: PRO61498
 Figure 287: DNA327550, NP_001959.1, 201435_s_at
 Figure 288: PRO81164
 Figure 289: DNA273396, DNA273396, 201449_at
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 Figure 292: DNA274343, NP_000894.1, 201467_s_at
 Figure 293: PRO62259
 Figure 294: DNA328413, NP_004823.1, 201470_at
 Figure 295: PRO84258
 Figure 296: DNA328414, NP_003891.1, 201471_s_at
 Figure 297: PRO81346
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 Figure 300: DNA88608, NP_002893.1, 201485_s_at
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 Figure 303: PRO37073
 Figure 304: DNA304459, NP_005720.1, 201490_s_at
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 Figure 306: DNA253807, NP_065390.1, 201502_s_at
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 Figure 308: DNA328415, BC006997, 201503_at
 Figure 309: PRO60207
 Figure 310: DNA328416, NP_002613.2, 201507_at
 Figure 311: PRO84259
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 Figure 314A-B: DNA150463, NP_055635.1, 201519_at
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 Figure 316: DNA328417, ATP6V1F, 201527_at
 Figure 317: PRO84260
 Figure 318: DNA328418, NP_003398.1, 201531_at
 Figure 319: PRO84261
 Figure 320: DNA328419, NP_002779.1, 201532_at
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 Figure 322: DNA328420, BC002682, 201537_s_at
 Figure 323: PRO58245
 Figure 324: DNA88464, NP_005552.2, 201551_s_at

Figure 325: PRO2804
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 Figure 328: DNA227071, NP_000260.1, 201577_at
 Figure 329: PRO37534
 Figure 330A-B: DNA227307, NP_009115.1, 201591_s_at
 Figure 331: PRO37770
 Figure 332: DNA255406, NP_005533.1, 201625_s_at
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 Figure 334A-B: DNA328421, 475621.10, 201646_at
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 Figure 338: DNA269791, NP_001168.1, 201659_s_at
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 Figure 345: PRO61148
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 Figure 349: PRO59538
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 Figure 355: PRO84264
 Figure 356: DNA328426, NP_000582.1, 201743_at
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 Figure 358: DNA150429, NP_002813.1, 201745_at
 Figure 359: PRO12769
 Figure 360: DNA272465, NP_004543.1, 201757_at
 Figure 361: PRO60713
 Figure 362: DNA328427, NP_061109.1, 201760_s_at
 Figure 363: PRO84265
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 Figure 365: PRO59136
 Figure 366: DNA323937, NP_005689.2, 201771_at
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 Figure 368: DNA88619, NP_002924.1, 201785_at
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 Figure 380: DNA328430, NP_005496.2, 201819_at
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 Figure 383: PRO80735
 Figure 384: DNA150650, NP_057086.1, 201825_s_at
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 Figure 400: DNA83046, NP_000565.1, 201926_s_at
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 Figure 402: DNA273014, NP_000117.1, 201931_at
 Figure 403: PRO61085
 Figure 404: DNA254147, NP_000512.1, 201944_at
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 Figure 406: DNA274167, NP_006422.1, 201946_s_at
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 Figure 423: DNA328435, NP_002481.1, 202001_s_at
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 Figure 471: DNA325823, NP_055702.1, 202258_s_at
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 Figure 473: DNA256533, NP_006105.1, 202264_s_at
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Figure 562: PRO61522
Figure 563: DNA328458, NP_037458.2, 202679_s_at
Figure 564: PRO84284
Figure 565: DNA84130, NP_003801.1, 202687_s_at
Figure 566: PRO1096
Figure 567: DNA271085, NP_004751.1, 202693_s_at
Figure 568: PRO59409
Figure 569A-B: DNA150467, NP_055513.1, 202699_s_at
Figure 570: PRO12272
Figure 571A-B: DNA328459, NP_004332.2, 202715_s_at
Figure 572: PRO84285
Figure 573: DNA273290, NP_002047.1, 202722_s_at
Figure 574: PRO61300
Figure 575: DNA328460, NP_004190.1, 202733_s_at
Figure 576: PRO84286
Figure 577: DNA150713, NP_006570.1, 202735_s_at
Figure 578: PRO12082
Figure 579A-B: DNA328461, 350230.2, 202741_s_at
Figure 580: PRO84287
Figure 581: DNA271973, NP_002722.1, 202742_s_at
Figure 582: PRO60248
Figure 583A-B: DNA150943, NP_036376.1, 202752_s_at
Figure 584: PRO12550
Figure 585A-C: DNA328462, HSA303079, 202759_s_at
Figure 586: PRO84288
Figure 587A-C: DNA328463, NP_009134.1, 202760_s_at
Figure 588: PRO84289
Figure 589: DNA226080, NP_001601.1, 202767_s_at
Figure 590: PRO36543
Figure 591A-B: DNA150977, NP_006723.1, 202768_s_at
Figure 592: PRO12828
Figure 593A-B: DNA328464, 977954.20, 202769_s_at
Figure 594: PRO84290
Figure 595: DNA226578, NP_004345.1, 202770_s_at
Figure 596: PRO37041
Figure 597A-B: DNA103521, NP_004163.1, 202800_s_at
Figure 598: PRO4848
Figure 599A-B: DNA327583, ABCC1, 202805_s_at
Figure 600: PRO83604
Figure 601: DNA328465, NP_005639.1, 202823_s_at
Figure 602: PRO84291
Figure 603: DNA225865, NP_004986.1, 202827_s_at
Figure 604: PRO36328
Figure 605: DNA225926, NP_000138.1, 202838_s_at
Figure 606: PRO36389
Figure 607: DNA328466, NP_004554.1, 202847_s_at
Figure 608: PRO84292
Figure 609: DNA103394, NP_004198.1, 202855_s_at
Figure 610: PRO4722
Figure 611: DNA275144, NP_000128.1, 202862_s_at
Figure 612: PRO62852
Figure 613: DNA328467, SP100, 202864_s_at
Figure 614: PRO84293
Figure 615: DNA287289, NP_058132.1, 202869_s_at
Figure 616: PRO69559
Figure 617: DNA328468, BC010960, 202872_s_at
Figure 618: PRO84294
Figure 619: DNA328469, NP_001686.1, 202874_s_at
Figure 620: PRO84295
Figure 621A-B: DNA255318, NP_036204.1, 202877_s_at
Figure 622: PRO50388
Figure 623A-B: DNA328470, NP_055620.1, 202909_s_at
Figure 624: PRO84296
Figure 625: DNA327584, NP_002955.2, 202917_s_at
Figure 626: PRO80649
Figure 627: DNA272425, NP_001489.1, 202923_s_at
Figure 628: PRO60677
Figure 629: DNA328471, ZMPSTE24, 202939_s_at
Figure 630: PRO84297
Figure 631: DNA269481, NP_001976.1, 202942_s_at
Figure 632: PRO57901
Figure 633: DNA328472, NP_000482.2, 202953_s_at
Figure 634: PRO84298
Figure 635A-B: DNA328473, NP_006473.1,

202968_s_at
 Figure 636: PRO84299
 Figure 637A-C: DNA328474, 1501914.1, 202969_at
 Figure 638: PRO84300
 Figure 639: DNA325915, ZAP128, 202982_s_at
 Figure 640: PRO82369
 Figure 641: DNA271272, NP_000366.1, 203031_s_at
 Figure 642: PRO59583
 Figure 643: DNA324049, FH, 203032_s_at
 Figure 644: PRO62607
 Figure 645A-B: DNA271865, NP_055566.1, 203037_s_at
 Figure 646: PRO60145
 Figure 647: DNA328475, LAMP2, 203042_at
 Figure 648: PRO84301
 Figure 649A-B: DNA328476, AF074331, 203058_s_at
 Figure 650: PRO84302
 Figure 651: DNA256830, NP_004815.1, 203100_s_at
 Figure 652: PRO51761
 Figure 653: DNA272867, NP_003960.1, 203109_at
 Figure 654: PRO60960
 Figure 655A-B: DNA227582, NP_000608.1, 203124_s_at
 Figure 656: PRO38045
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 Figure 658: PRO84303
 Figure 659A-B: DNA328478, NP_055720.2, 203158_s_at
 Figure 660: PRO84304
 Figure 661: DNA226136, NP_003246.1, 203167_at
 Figure 662: PRO36599
 Figure 663: DNA328479, NP_001473.1, 203178_at
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 Figure 665A-C: DNA328480, NP_001990.1, 203184_at
 Figure 666: PRO84306
 Figure 667A-B: DNA271010, NP_055552.1, 203185_at
 Figure 668: PRO59339
 Figure 669: DNA270448, NP_002487.1, 203189_s_at
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 Figure 671A-B: DNA328481, MTMR2, 203211_s_at
 Figure 672: PRO84307
 Figure 673A-C: DNA328482, NP_000426.1, 203238_s_at
 Figure 674: PRO84308
 Figure 675: DNA328483, NP_061163.1, 203255_at
 Figure 676: PRO84309
 Figure 677: DNA227127, NP_003571.1, 203269_at
 Figure 678: PRO37590
 Figure 679: DNA328484, UNC119, 203271_s_at
 Figure 680: PRO84310
 Figure 681: DNA302020, NP_005564.1, 203276_at
 Figure 682: PRO70993
 Figure 683A-B: DNA328485, BHC80, 203278_s_at
 Figure 684: PRO84311
 Figure 685: DNA328486, NP_000149.1, 203282_at
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 Figure 689: DNA328488, NP_003907.2, 203300_x_at
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 Figure 691: DNA328489, NP_006511.1, 203303_at
 Figure 692: PRO84314
 Figure 693A-B: DNA328490, NP_000120.1, 203305_at
 Figure 694: PRO84315
 Figure 695: DNA327593, NP_006205.1, 203335_at
 Figure 696: PRO59733
 Figure 697: DNA328491, ICAP-1A, 203336_s_at
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 Figure 699A-B: DNA328492, NP_056125.1, 203354_s_at
 Figure 700: PRO84316
 Figure 701: DNA328493, NP_008957.1, 203367_at
 Figure 702: PRO84317
 Figure 703: DNA328494, RPS6KA1, 203379_at
 Figure 704: PRO84318
 Figure 705: DNA274960, NP_008856.1, 203380_x_at
 Figure 706: PRO62694
 Figure 707: DNA88084, NP_000032.1, 203381_s_at
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 Figure 709A-B: DNA254616, NP_004473.1, 203397_s_at
 Figure 710: PRO49718
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 Figure 713: DNA323927, NP_005563.1, 203411_s_at
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 Figure 715: DNA151037, NP_036461.1, 203414_at
 Figure 716: PRO12586
 Figure 717: DNA273410, NP_004036.1, 203454_s_at
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 Figure 721: DNA328496, NP_002428.1, 203466_at
 Figure 722: PRO80786
 Figure 723A-B: DNA255622, NP_009187.1, 203472_s_at
 Figure 724: PRO50686
 Figure 725A-C: DNA328497, NP_005493.1, 203504_s_at
 Figure 726: PRO84319
 Figure 727A-C: DNA328498, AF285167, 203505_at
 Figure 728: PRO84320
 Figure 729A-B: DNA188400, NP_001057.1, 203508_at
 Figure 730: PRO21928
 Figure 731A-B: DNA328499, NP_003096.1, 203509_at
 Figure 732: PRO84321
 Figure 733: DNA272911, NP_006545.1, 203517_at
 Figure 734: PRO60997
 Figure 735A-D: DNA328500, NP_000072.1, 203518_at
 Figure 736: PRO84322
 Figure 737A-B: DNA103296, NP_006369.1, 203528_at

Figure 738: PRO4626
Figure 739: DNA323910, NP_002956.1, 203535_at
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Figure 741A-B: DNA272399, NP_001197.1, 203543_s_at
Figure 742: PRO60653
Figure 743: DNA328501, NP_076984.1, 203545_at
Figure 744: PRO84323
Figure 745: DNA88453, NP_000228.1, 203548_s_at
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Figure 748: PRO84324
Figure 749: DNA328503, NP_000272.1, 203557_s_at
Figure 750: PRO10850
Figure 751: DNA327594, NP_003869.1, 203560_at
Figure 752: PRO83611
Figure 753: DNA225916, NP_067674.1, 203561_at
Figure 754: PRO36379
Figure 755: DNA273676, NP_055488.1, 203584_at
Figure 756: PRO61644
Figure 757: DNA83085, NP_000751.1, 203591_s_at
Figure 758: PRO2583
Figure 759: DNA271003, NP_003720.1, 203594_at
Figure 760: PRO59332
Figure 761A-B: DNA328504, 1400155.1, 203608_at
Figure 762: PRO84325
Figure 763: DNA328505, NP_002484.1, 203613_s_at
Figure 764: PRO62117
Figure 765: DNA328506, NP_001046.1, 203615_x_at
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Figure 767: DNA225774, NP_005079.1, 203624_at
Figure 768: PRO36237
Figure 769: DNA254642, NP_004100.1, 203646_at
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Figure 771: DNA328507, NP_006395.1, 203650_at
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Figure 773A-B: DNA272998, NP_055548.1, 203651_at
Figure 774: PRO61070
Figure 775: DNA328508, NP_003368.1, 203683_s_at
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Figure 777: DNA255298, NP_004394.1, 203695_s_at
Figure 778: PRO50371
Figure 779: DNA227020, NP_001416.1, 203729_at
Figure 780: PRO37483
Figure 781: DNA328509, NP_006739.1, 203760_s_at
Figure 782: PRO57996
Figure 783: DNA328510, NP_055066.1, 203775_at
Figure 784: PRO84327
Figure 785A-B: DNA194602, NP_006370.1, 203789_s_at
Figure 786: PRO23944
Figure 787: DNA328511, NP_031397.1, 203825_at
Figure 788: PRO57838
Figure 789A-B: DNA328512, NP_005772.2, 203839_s_at
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Figure 791A-B: DNA272451, HSU86453, 203879_at
Figure 792: PRO60700
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Figure 794: PRO2558
Figure 795: DNA328513, NP_057367.1, 203893_at
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Figure 797: DNA150974, NP_005684.1, 203920_at
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Figure 802: PRO2711
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Figure 804: PRO37695
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Figure 807: DNA328515, NP_000775.1, 203979_at
Figure 808: PRO84330
Figure 809: DNA327608, NP_001433.1, 203980_at
Figure 810: PRO83617
Figure 811: DNA328516, NP_005833.1, 204011_at
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Figure 813: DNA328517, NP_003558.1, 204032_at
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Figure 815: DNA226342, NP_000305.1, 204054_at
Figure 816: PRO36805
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Figure 822: PRO37200
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Figure 825: DNA328520, NP_079353.1, 204080_at
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Figure 827A-B: DNA150739, NP_006484.1, 204084_s_at
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Figure 829: DNA227130, NP_002551.1, 204088_at
Figure 830: PRO37593
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Figure 835: DNA328523, NP_006712.1, 204119_s_at
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Figure 839: DNA328525, BC021224, 204131_s_at
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Figure 841: DNA103532, NP_003263.1, 204137_at
Figure 842: PRO4859
Figure 843: DNA324816, NP_001060.1, 204141_at
Figure 844: PRO81429

Figure 845: DNA270524, NP_059982.1, 204142_at
 Figure 846: PRO58901
 Figure 847: DNA328526, NP_000841.1, 204149_s_at
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 Figure 853: DNA328528, MLC1SA, 204173_at
 Figure 854: PRO60636
 Figure 855: DNA328529, NP_001620.2, 204174_at
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 Figure 863: DNA270434, NP_006434.1, 204238_s_at
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 Figure 867A-B: DNA188734, NP_001261.1, 204258_at
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 Figure 879: DNA225750, NP_000254.1, 204360_s_at
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 Figure 950: DNA225661, NP_001944.1, 204858_s_at

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 Figure 952: DNA328545, NP_064525.1, 204859_s_at
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 Figure 1058A-B: DNA327643, NP_055712.1, 205594_at
 Figure 1059: PRO83644
 Figure 1060A-C: DNA328568, NP_006720.1, 205603_s_at
 Figure 1061: PRO59731
 Figure 1062: DNA324324, NP_000679.1, 205633_s_at
 Figure 1063: PRO81000
 Figure 1064: DNA328569, NP_077274.1, 205634_x_at
 Figure 1065: PRO84365
 Figure 1066: DNA88076, NP_001628.1, 205639_at
 Figure 1067: PRO2640
 Figure 1068: DNA287317, NP_003724.1, 205660_at
 Figure 1069: PRO69582
 Figure 1070: DNA328570, NP_004040.1, 205681_at
 Figure 1071: PRO37843
 Figure 1072: DNA327644, NP_060395.2, 205684_s_at
 Figure 1073: PRO83645
 Figure 1074: DNA150621, NP_036595.1, 205704_s_at
 Figure 1075: PRO12374
 Figure 1076: DNA328571, NP_001254.1, 205709_s_at
 Figure 1077: PRO84366
 Figure 1078: DNA88106, NP_004325.1, 205715_at
 Figure 1079: PRO2655
 Figure 1080: DNA270401, NP_003140.1, 205743_at
 Figure 1081: PRO58784
 Figure 1082: DNA275620, NP_000628.1, 205770_at
 Figure 1083: PRO63244
 Figure 1084: DNA88187, NP_001757.1, 205789_at
 Figure 1085: PRO2689
 Figure 1086: DNA76517, NP_002176.1, 205798_at
 Figure 1087: PRO2541
 Figure 1088A-B: DNA271915, NP_056191.1, 205801_s_at
 Figure 1089: PRO60192
 Figure 1090: DNA194766, NP_079504.1, 205804_s_at
 Figure 1091: PRO24046
 Figure 1092: DNA328572, NP_004309.2, 205808_at
 Figure 1093: PRO84367
 Figure 1094: DNA328573, NP_006761.1, 205819_at
 Figure 1095: PRO1559
 Figure 1096A-B: DNA328574, NP_004963.1, 205842_s_at
 Figure 1097: PRO84368
 Figure 1098: DNA327651, NP_005612.1, 205863_at
 Figure 1099: PRO83649
 Figure 1100: DNA328575, NP_071754.2, 205872_x_at
 Figure 1101: PRO84369
 Figure 1102A-B: DNA220746, NP_000876.1, 205884_at
 Figure 1103: PRO34724
 Figure 1104A-B: DNA273962, NP_055605.1, 205888_s_at
 Figure 1105: PRO61910
 Figure 1106: DNA93423, NP_000667.1, 205891_at
 Figure 1107: PRO4944
 Figure 1108: DNA328576, HSU20350, 205898_at
 Figure 1109: PRO4940
 Figure 1110: DNA328577, NP_003905.1, 205899_at
 Figure 1111: PRO59588
 Figure 1112A-B: DNA196549, NP_003034.1, 205920_at
 Figure 1113: PRO25031
 Figure 1114: DNA328578, NP_004656.2, 205922_at
 Figure 1115: PRO7426
 Figure 1116A-B: DNA270867, NP_006217.1, 205934_at
 Figure 1117: PRO59203
 Figure 1118: DNA76516, NP_000556.1, 205945_at
 Figure 1119: PRO2022
 Figure 1120: DNA196439, NP_003865.1, 205988_at
 Figure 1121: PRO24934
 Figure 1122: DNA36722, NP_000576.1, 205992_s_at
 Figure 1123: PRO77
 Figure 1124: DNA328579, BC020082, 206020_at
 Figure 1125: PRO84370
 Figure 1126: DNA328580, HSU27699, 206058_at
 Figure 1127: PRO4627
 Figure 1128: DNA328581, NP_002122.1, 206074_s_at
 Figure 1129: PRO34536
 Figure 1130: DNA328582, NP_001865.1, 206100_at
 Figure 1131: PRO84371
 Figure 1132: DNA226105, NP_002925.1, 206111_at
 Figure 1133: PRO36568
 Figure 1134: DNA225764, NP_000037.1, 206129_s_at
 Figure 1135: PRO36227
 Figure 1136: DNA328583, ASGR2, 206130_s_at
 Figure 1137: PRO84372
 Figure 1138: DNA327656, NP_055294.1, 206134_at
 Figure 1139: PRO36117
 Figure 1140A-B: DNA271837, NP_055497.1, 206135_at
 Figure 1141: PRO60117
 Figure 1142: DNA328584, NP_001148.1, 206200_s_at
 Figure 1143: PRO4833
 Figure 1144: DNA226058, NP_005075.1, 206214_at
 Figure 1145: PRO36521
 Figure 1146: DNA218691, NP_003832.1, 206222_at
 Figure 1147: PRO34469
 Figure 1148A-C: DNA328585, AF286028, 206239_s_at
 Figure 1149: DNA328586, NP_002369.2, 206267_s_at
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 Figure 1151: DNA328587, NP_002612.1, 206380_s_at
 Figure 1152: PRO2854
 Figure 1153: DNA255814, NP_005840.1, 206420_at
 Figure 1154: PRO50869
 Figure 1155: DNA328588, NP_060823.1, 206500_s_at
 Figure 1156: PRO84374
 Figure 1157: DNA270444, NP_004824.1, 206513_at
 Figure 1158: PRO58823

Figure 1159: DNA196614, NP_001158.1, 206536_s_at
Figure 1160: PRO25091
Figure 1161: DNA270019, NP_036351.1, 206538_at
Figure 1162: PRO58414
Figure 1163: DNA327663, NP_006771.1, 206565_x_at
Figure 1164: PRO83654
Figure 1165: DNA327665, NP_002099.1, 206643_at
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Figure 1167: DNA328589, BCL2L1, 206665_s_at
Figure 1168: PRO83141
Figure 1169: DNA328590, C6orf32, 206707_x_at
Figure 1170: PRO84375
Figure 1171A-B: DNA88191, NP_001234.1, 206729_at
Figure 1172: PRO2691
Figure 1173: DNA327669, NP_000914.1, 206792_x_at
Figure 1174: PRO83657
Figure 1175: DNA270107, NP_006856.1, 206881_s_at
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Figure 1177: DNA256561, NP_062550.1, 206914_at
Figure 1178: PRO51592
Figure 1179: DNA328591, NP_006635.1, 206976_s_at
Figure 1180: PRO84376
Figure 1181A-B: DNA227659, NP_000570.1, 206991_s_at
Figure 1182: PRO38122
Figure 1183: DNA188289, NP_001548.1, 207008_at
Figure 1184: PRO21820
Figure 1185: DNA328592, AB015228, 207016_s_at
Figure 1186: PRO84377
Figure 1187: DNA227531, NP_004722.1, 207057_at
Figure 1188: PRO37994
Figure 1189: DNA327673, NP_002188.1, 207071_s_at
Figure 1190: PRO83660
Figure 1191A-B: DNA328593, CIAS1, 207075_at
Figure 1192: PRO84378
Figure 1193A-B: DNA328594, CSF1, 207082_at
Figure 1194: PRO84379
Figure 1195: DNA88291, NP_001965.1, 207111_at
Figure 1196: PRO2729
Figure 1197A-B: DNA327674, NP_002739.1, 207121_s_at
Figure 1198: PRO83661
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Figure 1200: PRO84380
Figure 1201: DNA226996, NP_000239.1, 207233_s_at
Figure 1202: PRO37459
Figure 1203A-B: DNA226536, NP_003225.1, 207332_s_at
Figure 1204: PRO36999
Figure 1205: DNA227668, NP_000158.1, 207387_s_at
Figure 1206: PRO38131
Figure 1207: DNA328596, DEGS, 207431_s_at
Figure 1208: PRO37741
Figure 1209: DNA274829, NP_003653.1, 207469_s_at
Figure 1210: PRO62588
Figure 1211: DNA328597, NP_001680.1, 207507_s_at
Figure 1212: PRO84381
Figure 1213: DNA328598, NP_055146.1, 207528_s_at
Figure 1214: PRO23276
Figure 1215: DNA328599, NFKB2, 207535_s_at
Figure 1216: PRO84382
Figure 1217: DNA328600, NP_004839.1, 207571_x_at
Figure 1218: PRO84383
Figure 1219: DNA328601, NP_056490.1, 207574_s_at
Figure 1220: PRO84384
Figure 1221: DNA328602, NP_002261.1, 207657_x_at
Figure 1222: PRO84385
Figure 1223: DNA226278, NP_005865.1, 207697_x_at
Figure 1224: PRO36741
Figure 1225: DNA227395, NP_005331.1, 207721_x_at
Figure 1226: PRO37858
Figure 1227: DNA325654, NP_054752.1, 207761_s_at
Figure 1228: PRO4348
Figure 1229: DNA226930, NP_004152.1, 207791_s_at
Figure 1230: PRO37393
Figure 1231: DNA328603, NP_000304.1, 207808_s_at
Figure 1232: PRO84386
Figure 1233: DNA328604, NP_001174.2, 207809_s_at
Figure 1234: PRO84387
Figure 1235: DNA327682, NP_001905.1, 207843_x_at
Figure 1236: PRO83666
Figure 1237: DNA36708, NP_002081.1, 207850_at
Figure 1238: PRO34256
Figure 1239: DNA199788, NP_002981.1, 207861_at
Figure 1240: PRO34107
Figure 1241: DNA328605, ST7, 207871_s_at
Figure 1242: PRO84388
Figure 1243: DNA256523, NP_006854.1, 207872_s_at
Figure 1244: PRO51557
Figure 1245: DNA218651, NP_003798.1, 207907_at
Figure 1246: PRO34447
Figure 1247: DNA275286, NP_009205.1, 208002_s_at
Figure 1248: PRO62967
Figure 1249A-B: DNA328606, CBFA2T3, 208056_s_at
Figure 1250: PRO84389
Figure 1251A-B: DNA328607, NP_003639.1, 208072_s_at
Figure 1252: PRO84390
Figure 1253: DNA327685, NP_067586.1, 208074_s_at
Figure 1254: PRO83669
Figure 1255: DNA328608, NP_006264.2, 208075_s_at
Figure 1256: PRO9932
Figure 1257: DNA255376, NP_110423.1, 208091_s_at
Figure 1258: PRO50444
Figure 1259: DNA327686, NP_005898.1, 208116_s_at
Figure 1260: PRO83670
Figure 1261A-B: DNA328609, NP_109592.1, 208121_s_at
Figure 1262: PRO84391
Figure 1263: DNA328610, NP_112601.1, 208146_s_at
Figure 1264: PRO84392
Figure 1265A-B: DNA226706, NP_003777.2,

208161_s_at
 Figure 1266: PRO37169
 Figure 1267: DNA328611, RASGRP2, 208206_s_at
 Figure 1268: PRO84393
 Figure 1269: DNA328612, NP_000166.2, 208308_s_at
 Figure 1270: PRO84394
 Figure 1271: DNA270558, NP_006734.1, 208319_s_at
 Figure 1272: PRO58933
 Figure 1273: DNA227614, NP_004859.1, 208336_s_at
 Figure 1274: PRO38077
 Figure 1275: DNA327690, NP_004022.1, 208436_s_at
 Figure 1276: PRO83673
 Figure 1277: DNA328613, NP_056953.2, 208510_s_at
 Figure 1278: PRO84395
 Figure 1279A-C: DNA328614, SRRM2, 208610_s_at
 Figure 1280: PRO84396
 Figure 1281A-C: DNA328615, NP_003118.1, 208611_s_at
 Figure 1282: PRO84397
 Figure 1283A-C: DNA328616, NP_001448.1, 208613_s_at
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 Figure 1285: DNA326362, VATI, 208626_s_at
 Figure 1286: PRO82758
 Figure 1287: DNA325912, NP_001093.1, 208637_x_at
 Figure 1288: PRO82367
 Figure 1289: DNA271268, NP_009057.1, 208649_s_at
 Figure 1290: PRO59579
 Figure 1291: DNA328617, AF299343, 208653_s_at
 Figure 1292: PRO84399
 Figure 1293A-C: DNA328618, NP_003307.2, 208664_s_at
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 Figure 1295: DNA304686, NP_002565.1, 208680_at
 Figure 1296: PRO71112
 Figure 1297: DNA304499, NP_006588.1, 208687_x_at
 Figure 1298: PRO71063
 Figure 1299A-B: DNA328619, BC001188, 208691_at
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 Figure 1301: DNA287189, NP_002038.1, 208693_s_at
 Figure 1302: PRO69475
 Figure 1303: DNA324217, ATIC, 208758_at
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 Figure 1305: DNA327696, AF228339, 208763_s_at
 Figure 1306: PRO83679
 Figure 1307: DNA328620, AK000295, 208772_at
 Figure 1308: PRO84402
 Figure 1309: DNA328621, NP_002788.1, 208799_at
 Figure 1310: PRO84403
 Figure 1311: DNA287169, CAA42052.1, 208805_at
 Figure 1312: PRO10404
 Figure 1313: DNA324531, NP_002120.1, 208808_s_at
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 Figure 1315: DNA273521, NP_002070.1, 208813_at
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 Figure 1317: DNA328622, BC000835, 208827_at
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 Figure 1320: PRO38019
 Figure 1321: DNA326042, NP_031390.1, 208837_at
 Figure 1322: PRO1078
 Figure 1323A-B: DNA328623, NP_056107.1, 208858_s_at
 Figure 1324: PRO61321
 Figure 1325: DNA227874, NP_003320.1, 208864_s_at
 Figure 1326: PRO38337
 Figure 1327: DNA328624, BC003562, 208891_at
 Figure 1328: PRO59076
 Figure 1329: DNA328625, NP_073143.1, 208892_s_at
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 Figure 1331: DNA328626, NP_057078.1, 208898_at
 Figure 1332: PRO61768
 Figure 1333: DNA327700, BC015130, 208905_at
 Figure 1334: PRO83683
 Figure 1335: DNA325472, NP_116056.2, 208906_at
 Figure 1336: PRO81995
 Figure 1337A-B: DNA328627, FLJ13052, 208918_s_at
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 Figure 1339: DNA325473, NP_006353.2, 208922_s_at
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 Figure 1341: DNA287238, NP_000425.1, 208926_at
 Figure 1342: PRO69515
 Figure 1343: DNA328628, NP_060542.2, 208933_s_at
 Figure 1344: PRO84406
 Figure 1345: DNA290261, NP_001291.2, 208960_s_at
 Figure 1346: PRO70387
 Figure 1347A-B: DNA325478, NP_037534.2, 208962_s_at
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 Figure 1349: DNA328629, NP_006079.1, 208977_x_at
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 Figure 1353: DNA328631, AK027318, 209006_s_at
 Figure 1354: PRO84409
 Figure 1355: DNA328632, DJ465N24.2.1Homo, 209007_s_at
 Figure 1356: DNA328633, NP_004784.2, 209017_s_at
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 Figure 1358A-B: DNA328634, NP_006594.1, 209023_s_at
 Figure 1359: PRO84412
 Figure 1360: DNA328635, BC020946, 209026_x_at
 Figure 1361: PRO84413
 Figure 1362: DNA274202, NP_006804.1, 209034_at
 Figure 1363: PRO62131
 Figure 1364: DNA328636, PAPSS1, 209043_at
 Figure 1365: PRO84414
 Figure 1366A-C: DNA328637, HSA7042, 209053_s_at
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 Figure 1368: DNA326406, NP_005315.1, 209069_s_at
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Figure 1370: DNA227289, NP_006532.1, 209080_x_at
Figure 1371: PRO37752
Figure 1372: DNA274180, NP_009005.1, 209083_at
Figure 1373: PRO62110
Figure 1374: DNA327707, NP_000148.1, 209093_s_at
Figure 1375: PRO83689
Figure 1376: DNA226564, NP_000099.1, 209095_at
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Figure 1381: PRO81129
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Figure 1383: PRO62502
Figure 1384: DNA328639, HSM801840, 209132_s_at
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Figure 1387: PRO84416
Figure 1388: DNA327713, BC010653, 209146_at
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Figure 1392: DNA328641, NP_001840.2, 209156_s_at
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Figure 1418A-C: DNA328647, AB017133, 209234_at
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Figure 1422: PRO84424
Figure 1423: DNA255255, NP_071437.1, 209267_s_at
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Figure 1425A-B: DNA226827, NP_001673.1, 209281_s_at
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Figure 1427: DNA328650, 200118.10, 209286_at
Figure 1428: PRO84425
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Figure 1430: PRO62628
Figure 1431: DNA328651, AF087853, 209305_s_at
Figure 1432: PRO82889
Figure 1433: DNA327718, CASP4, 209310_s_at
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Figure 1435: DNA328652, NP_077298.1, 209321_s_at
Figure 1436: PRO84426
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Figure 1440: PRO84428
Figure 1441: DNA328655, 346677.3, 209341_s_at
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Figure 1443: DNA269630, NP_003281.1, 209344_at
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Figure 1449A-B: DNA328658, AF055376, 209348_s_at
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Figure 1457: DNA275366, BC001851, 209444_at
Figure 1458: PRO63036
Figure 1459: DNA328660, NP_003675.2, 209467_s_at
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Figure 1461A-B: DNA328661, NP_006304.1, 209475_at
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Figure 1463: DNA328662, OSBPL1A, 209485_s_at
Figure 1464: PRO84436
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Figure 1469: DNA328663, NP_057157.1, 209524_at
Figure 1470: PRO36183
Figure 1471A-C: DNA328664, NP_009131.1, 209534_x_at
Figure 1472: PRO84437
Figure 1473A-B: DNA328665, RGL, 209568_s_at

Figure 1474: PRO84438
 Figure 1475: DNA328666, AF084943, 209585_s_at
 Figure 1476: PRO1917
 Figure 1477: DNA328667, S69189, 209600_s_at
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 Figure 1558: PRO37964
 Figure 1559: DNA328687, AF004231, 210146_x_at
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 Figure 1562: PRO84457
 Figure 1563: DNA328689, NP_003259.2, 210166_at
 Figure 1564: PRO7521
 Figure 1565: DNA270196, HUMZFM1B, 210172_at
 Figure 1566: PRO58584
 Figure 1567: DNA328690, NP_524145.1, 210240_s_at
 Figure 1568: PRO59660
 Figure 1569: DNA326963, HRIHFB2122, 210276_s_at
 Figure 1570: PRO83276
 Figure 1571: DNA328691, NP_065717.1, 210346_s_at
 Figure 1572: PRO84458
 Figure 1573: DNA227652, NP_002549.1, 210401_at
 Figure 1574: PRO38115
 Figure 1575: DNA225514, NP_003864.1, 210510_s_at
 Figure 1576: PRO35977
 Figure 1577: DNA216517, NP_005055.1, 210549_s_at
 Figure 1578: PRO34269
 Figure 1579: DNA327746, HUMGCBA, 210589_s_at

Figure 1580: PRO83720
 Figure 1581: DNA328692, AF025529, 210660_s_at
 Figure 1582: PRO84459
 Figure 1583: DNA272127, NP_003928.1, 210663_s_at
 Figure 1584: PRO60397
 Figure 1585: DNA326525, NP_006330.1, 210719_s_at
 Figure 1586: PRO82894
 Figure 1587: DNA226183, NP_001453.1, 210773_s_at
 Figure 1588: PRO36646
 Figure 1589: DNA226078, NP_000296.1, 210830_s_at
 Figure 1590: PRO36541
 Figure 1591: DNA226152, NP_002650.1, 210845_s_at
 Figure 1592: PRO36615
 Figure 1593: DNA328693, HSU03891, 210873_x_at
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 Figure 1595: DNA328694, BC007810, 210944_s_at
 Figure 1596: PRO84461
 Figure 1597: DNA213676, NP_004604.1, 211003_x_at
 Figure 1598: PRO35142
 Figure 1599: DNA328695, NP_002145.1, 211015_s_at
 Figure 1600: PRO61480
 Figure 1601: DNA328696, NP_009214.1, 211026_s_at
 Figure 1602: PRO62720
 Figure 1603: DNA328697, NP_116112.1, 211038_s_at
 Figure 1604: PRO84462
 Figure 1605: DNA328698, BC006403, 211063_s_at
 Figure 1606: PRO12168
 Figure 1607: DNA326712, NP_001285.1, 211136_s_at
 Figure 1608: PRO83054
 Figure 1609A-B: DNA328699, AF189723, 211137_s_at
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 Figure 1611: DNA327752, HSDHACTYL, 211150_s_at
 Figure 1612A-B: DNA328700, SCD, 211162_x_at
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 Figure 1614: DNA328701, PSEN2, 211373_s_at
 Figure 1615: PRO80745
 Figure 1616: DNA328702, NP_036519.1, 211413_s_at
 Figure 1617: PRO84465
 Figure 1618: DNA256637, NP_008849.1, 211423_s_at
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 Figure 1620: DNA328703, NP_003956.1, 211434_s_at
 Figure 1621: PRO1873
 Figure 1622: DNA327755, NP_115957.1, 211458_s_at
 Figure 1623: PRO83725
 Figure 1624A-B: DNA328704, FGFR1, 211535_s_at
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 Figure 1626: DNA324626, RIL, 211564_s_at
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 Figure 1628: DNA328705, NP_001345.1, 211653_x_at
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 Figure 1632A-B: DNA328707, AF172264, 211828_s_at
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 Figure 1634: DNA226582, NP_003863.1, 211844_s_at
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 Figure 1637: PRO12756
 Figure 1638: DNA325941, NP_005339.1, 211968_s_at
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 Figure 1640: DNA287433, NP_006810.1, 212009_s_at
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 Figure 1643: PRO84467
 Figure 1644: DNA103380, NP_003365.1, 212038_s_at
 Figure 1645: PRO4710
 Figure 1646: DNA328709, BC004151, 212048_s_at
 Figure 1647: PRO37676
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 Figure 1655: DNA328712, NP_006501.1, 212118_s_at
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 Figure 1659: DNA328714, HSM801966, 212146_s_at
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 Figure 1662: DNA88630, AAA52701.1, 212154_s_at
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 Figure 1709: DNA151348, DNA151348, 212463_at
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 Figure 1717: DNA328732, NP_116193.1, 212502_at
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 Figure 2052: DNA328838, NP_054797.2, 218049_s_at
 Figure 2053: PRO70319
 Figure 2054: DNA328839, NP_057180.1, 218059_at
 Figure 2055: PRO84573
 Figure 2056: DNA328840, NP_060481.1, 218067_s_at
 Figure 2057: PRO84574
 Figure 2058: DNA328841, NP_060557.2, 218073_s_at
 Figure 2059: PRO84575
 Figure 2060A-C: DNA328842, 235943.8, 218098_at
 Figure 2061: PRO84576
 Figure 2062: DNA328843, NP_060939.1, 218099_at
 Figure 2063: PRO84577
 Figure 2064: DNA328844, NP_061156.1, 218111_s_at
 Figure 2065: PRO82111
 Figure 2066: DNA227498, NP_002125.3, 218120_s_at
 Figure 2067: PRO37961
 Figure 2068: DNA328845, NP_060615.1, 218126_at
 Figure 2069: PRO10274
 Figure 2070: DNA227264, LOC51312, 218136_s_at
 Figure 2071: PRO37727
 Figure 2072: DNA327857, NP_057386.1, 218142_s_at
 Figure 2073: PRO83799
 Figure 2074: DNA325852, NP_078813.1, 218153_at
 Figure 2075: PRO82314
 Figure 2076: DNA328846, NP_060522.2, 218169_at
 Figure 2077: PRO84578
 Figure 2078: DNA228094, NP_079416.1, 218175_at
 Figure 2079: PRO38557
 Figure 2080: DNA328847, NP_056338.1, 218194_at
 Figure 2081: PRO84579
 Figure 2082: DNA150593, NP_054747.1, 218196_at
 Figure 2083: PRO12353
 Figure 2084: DNA256555, NP_060042.1, 218205_s_at
 Figure 2085: PRO51586
 Figure 2086: DNA328848, NP_004522.1, 218212_s_at
 Figure 2087: PRO84580
 Figure 2088: DNA271622, NP_006020.3, 218224_at
 Figure 2089: PRO59909
 Figure 2090: DNA324353, NP_004538.2, 218226_s_at
 Figure 2091: PRO81026
 Figure 2092: DNA328849, NP_057075.1, 218232_at
 Figure 2093: PRO4382
 Figure 2094: DNA328850, NP_057187.1, 218254_s_at
 Figure 2095: PRO84581
 Figure 2096: DNA273230, NP_060914.1, 218273_s_at
 Figure 2097: PRO61257
 Figure 2098: DNA328851, NP_068590.1, 218276_s_at
 Figure 2099: PRO84582

Figure 2100: DNA323953, NP_003507.1, 218280_x_at
 Figure 2101: PRO80685
 Figure 2102: DNA254824, AF267865, 218294_s_at
 Figure 2103: PRO49920
 Figure 2104A-B: DNA328852, NP_003609.2, 218311_at
 Figure 2105: PRO84583
 Figure 2106A-B: DNA328853, NP_065702.2, 218319_at
 Figure 2107: PRO84584
 Figure 2108: DNA328854, NP_056979.1, 218350_s_at
 Figure 2109: PRO84585
 Figure 2110: DNA328855, NP_076952.1, 218375_at
 Figure 2111: PRO9771
 Figure 2112: DNA328856, NP_068376.1, 218380_at
 Figure 2113: PRO84586
 Figure 2114: DNA328857, NP_037481.1, 218407_x_at
 Figure 2115: PRO84587
 Figure 2116: DNA324953, NP_057412.1, 218412_s_at
 Figure 2117: PRO81550
 Figure 2118A-B: DNA255062, NP_060704.1, 218424_s_at
 Figure 2119: PRO50149
 Figure 2120: DNA150661, NP_057162.1, 218446_s_at
 Figure 2121: PRO12398
 Figure 2122: DNA326218, NP_064573.1, 218447_at
 Figure 2123: PRO82631
 Figure 2124: DNA328858, HEBP1, 218450_at
 Figure 2125: PRO84588
 Figure 2126: DNA327942, NP_060596.1, 218465_at
 Figure 2127: PRO83870
 Figure 2128: DNA328859, AF154054, 218468_s_at
 Figure 2129: PRO1608
 Figure 2130A-B: DNA328860, NP_037504.1, 218469_at
 Figure 2131: PRO1608
 Figure 2132: DNA328861, NP_057030.2, 218472_s_at
 Figure 2133: PRO84589
 Figure 2134: DNA328862, NP_057626.2, 218499_at
 Figure 2135: PRO84590
 Figure 2136: DNA328863, NP_060264.1, 218503_at
 Figure 2137: PRO84591
 Figure 2138: DNA328864, NP_060726.2, 218512_at
 Figure 2139: PRO84592
 Figure 2140: DNA255432, NP_060283.1, 218516_s_at
 Figure 2141: PRO50499
 Figure 2142: DNA194326, NP_065713.1, 218538_s_at
 Figure 2143: PRO23708
 Figure 2144: DNA328865, NP_064587.1, 218557_at
 Figure 2145: PRO84593
 Figure 2146: DNA328866, NP_005691.1, 218567_x_at
 Figure 2147: PRO69644
 Figure 2148: DNA328867, NP_085053.1, 218600_at
 Figure 2149: PRO84594
 Figure 2150: DNA328868, NP_057629.1, 218611_at
 Figure 2151: PRO84595
 Figure 2152: DNA328869, NP_060892.1, 218613_at
 Figure 2153: PRO84596
 Figure 2154: DNA328870, NP_060639.1, 218614_at
 Figure 2155: PRO84597
 Figure 2156: DNA256870, NP_073600.1, 218618_s_at
 Figure 2157: PRO51800
 Figure 2158: DNA254898, NP_060840.1, 218627_at
 Figure 2159: PRO49988
 Figure 2160: DNA328871, NP_068378.1, 218631_at
 Figure 2161: PRO84598
 Figure 2162: DNA328872, NP_036528.1, 218634_at
 Figure 2163: PRO84599
 Figure 2164: DNA328873, NP_057041.1, 218698_at
 Figure 2165: PRO84600
 Figure 2166: DNA324621, NP_054754.1, 218705_s_at
 Figure 2167: PRO1285
 Figure 2168: DNA328874, NP_054778.1, 218723_s_at
 Figure 2169: PRO84601
 Figure 2170: DNA328875, NP_064554.2, 218729_at
 Figure 2171: PRO84602
 Figure 2172: DNA328876, NP_060582.1, 218772_x_at
 Figure 2173: PRO84603
 Figure 2174: DNA328877, BC020507, 218821_at
 Figure 2175: PRO84604
 Figure 2176: DNA328878, NP_060104.1, 218823_s_at
 Figure 2177: PRO84605
 Figure 2178: DNA328879, NP_064570.1, 218845_at
 Figure 2179: PRO84606
 Figure 2180: DNA227367, NP_062456.1, 218853_s_at
 Figure 2181: PRO37830
 Figure 2182: DNA327872, NP_057713.1, 218856_at
 Figure 2183: PRO83812
 Figure 2184: DNA328880, NP_060369.1, 218872_at
 Figure 2185: PRO84607
 Figure 2186: DNA328881, NP_057706.1, 218890_x_at
 Figure 2187: PRO49469
 Figure 2188: DNA287166, NP_055129.1, 218943_s_at
 Figure 2189: PRO69459
 Figure 2190: DNA328882, NP_109589.1, 218967_s_at
 Figure 2191: PRO61822
 Figure 2192: DNA327211, NP_075053.1, 218989_x_at
 Figure 2193: PRO71052
 Figure 2194: DNA255929, NP_060935.1, 218992_at
 Figure 2195: PRO50982
 Figure 2196: DNA328883, NP_037474.1, 218996_at
 Figure 2197: PRO84608
 Figure 2198: DNA227194, FLJ11000, 218999_at
 Figure 2199: PRO37657
 Figure 2200: DNA328884, NP_054884.1, 219006_at
 Figure 2201: PRO84609
 Figure 2202: DNA227187, NP_057703.1, 219014_at
 Figure 2203: PRO37650
 Figure 2204: DNA328885, NP_061108.2, 219017_at
 Figure 2205: PRO50294
 Figure 2206A-B: DNA255239, NP_004832.1, 219026_s_at

Figure 2207: PRO50316
 Figure 2208: DNA328886, NP_078811.1, 219040_at
 Figure 2209: PRO84610
 Figure 2210: DNA328887, NP_061907.1, 219045_at
 Figure 2211: PRO84611
 Figure 2212: DNA328888, NP_060436.1, 219053_s_at
 Figure 2213: PRO84612
 Figure 2214: DNA328889, NP_006005.1, 219061_s_at
 Figure 2215: PRO84613
 Figure 2216: DNA328890, NP_060403.1, 219093_at
 Figure 2217: PRO84614
 Figure 2218: DNA327877, NP_065108.1, 219099_at
 Figure 2219: PRO83816
 Figure 2220: DNA328891, NP_060263.1, 219143_s_at
 Figure 2221: PRO84615
 Figure 2222: DNA210216, NP_006860.1, 219150_s_at
 Figure 2223: PRO33752
 Figure 2224: DNA328892, NP_067643.2, 219165_at
 Figure 2225: PRO84616
 Figure 2226A-B: DNA328893, NP_065699.1, 219201_s_at
 Figure 2227: PRO9914
 Figure 2228: DNA287235, NP_060598.1, 219204_s_at
 Figure 2229: PRO69514
 Figure 2230: DNA225594, NP_037404.1, 219229_at
 Figure 2231: PRO36057
 Figure 2232: DNA328894, NP_060796.1, 219243_at
 Figure 2233: PRO84617
 Figure 2234: DNA328895, NP_071762.2, 219259_at
 Figure 2235: PRO1317
 Figure 2236: DNA328896, NP_079037.1, 219265_at
 Figure 2237: PRO84618
 Figure 2238: DNA328897, TRPV2, 219282_s_at
 Figure 2239: PRO12382
 Figure 2240: DNA273489, NP_055210.1, 219290_x_at
 Figure 2241: PRO61472
 Figure 2242A-B: DNA328898, NP_060261.1, 219316_s_at
 Figure 2243: PRO84619
 Figure 2244: DNA328899, NP_061024.1, 219326_s_at
 Figure 2245: PRO84620
 Figure 2246A-B: DNA255889, NP_061764.1, 219340_s_at
 Figure 2247: PRO50942
 Figure 2248: DNA328900, NP_060814.1, 219344_at
 Figure 2249: PRO84621
 Figure 2250: DNA254518, NP_057354.1, 219371_s_at
 Figure 2251: PRO49625
 Figure 2252: DNA188342, NP_064510.1, 219385_at
 Figure 2253: PRO21718
 Figure 2254: DNA256417, NP_077271.1, 219402_s_at
 Figure 2255: PRO51457
 Figure 2256A-B: DNA327887, NP_006656.1, 219403_s_at
 Figure 2257: PRO83823
 Figure 2258: DNA327888, NP_071732.1, 219412_at

Figure 2259: PRO83824
 Figure 2260: DNA328901, FLJ20533, 219449_s_at
 Figure 2261: PRO84622
 Figure 2262: DNA328902, NP_071750.1, 219452_at
 Figure 2263: PRO84623
 Figure 2264: DNA328903, NP_002805.1, 219485_s_at
 Figure 2265: PRO84624
 Figure 2266: DNA328904, NP_076941.1, 219491_at
 Figure 2267: PRO84625
 Figure 2268A-B: DNA328905, NP_075392.1, 219496_at
 Figure 2269: PRO84626
 Figure 2270: DNA328906, NP_078855.1, 219506_at
 Figure 2271: PRO84627
 Figure 2272: DNA328907, NP_000067.1, 219534_x_at
 Figure 2273: PRO84628
 Figure 2274: DNA328908, 7691567.2, 219540_at
 Figure 2275: PRO84629
 Figure 2276: DNA225636, NP_065696.1, 219557_s_at
 Figure 2277: PRO36099
 Figure 2278A-B: DNA328909, NP_078800.2, 219558_at
 Figure 2279: PRO84630
 Figure 2280: DNA328910, NP_057666.1, 219593_at
 Figure 2281: PRO38848
 Figure 2282: DNA328911, MS4A4A, 219607_s_at
 Figure 2283: PRO84631
 Figure 2284: DNA328912, NP_060287.1, 219622_at
 Figure 2285: PRO84632
 Figure 2286: DNA328913, NP_079213.1, 219631_at
 Figure 2287: PRO84633
 Figure 2288: DNA328914, NP_060883.1, 219634_at
 Figure 2289: PRO36664
 Figure 2290: DNA327892, NP_060470.1, 219648_at
 Figure 2291: PRO83828
 Figure 2292: DNA328915, NP_055056.2, 219654_at
 Figure 2293: PRO84634
 Figure 2294: DNA228002, NP_071744.1, 219666_at
 Figure 2295: PRO38465
 Figure 2296: DNA328916, NP_071932.1, 219678_x_at
 Figure 2297: PRO84635
 Figure 2298: DNA287206, NP_060124.1, 219691_at
 Figure 2299: PRO69488
 Figure 2300: DNA328917, NP_061838.1, 219725_at
 Figure 2301: PRO7306
 Figure 2302: DNA328918, NP_078935.1, 219770_at
 Figure 2303: PRO84636
 Figure 2304: DNA328919, NP_078987.1, 219777_at
 Figure 2305: PRO84637
 Figure 2306: DNA227152, NP_038467.1, 219788_at
 Figure 2307: PRO37615
 Figure 2308: DNA328920, NP_061129.1, 219837_s_at
 Figure 2309: PRO4425
 Figure 2310: DNA256033, NP_060164.1, 219858_s_at
 Figure 2311: PRO51081
 Figure 2312: DNA254838, NP_078904.1, 219874_at

Figure 2313: PRO49933
 Figure 2314: DNA328921, NP_057079.1, 219878_s_at
 Figure 2315: PRO84638
 Figure 2316: DNA256325, NP_005470.1, 219889_at
 Figure 2317: PRO51367
 Figure 2318: DNA328922, NP_037384.1, 219890_at
 Figure 2319: PRO84639
 Figure 2320: DNA328923, NP_075379.1, 219892_at
 Figure 2321: PRO84640
 Figure 2322: DNA256608, NP_060408.1, 219895_at
 Figure 2323: PRO51611
 Figure 2324: DNA328924, NP_057150.2, 219933_at
 Figure 2325: PRO84641
 Figure 2326: DNA255456, NP_057268.1, 219947_at
 Figure 2327: PRO50523
 Figure 2328: DNA227804, NP_065394.1, 219952_s_at
 Figure 2329: PRO38267
 Figure 2330: DNA328925, NP_076403.1, 220005_at
 Figure 2331: PRO84642
 Figure 2332: DNA256467, NP_079054.1, 220009_at
 Figure 2333: PRO51504
 Figure 2334A-B: DNA292946, NP_061160.1, 220023_at
 Figure 2335: PRO70613
 Figure 2336: DNA171414, NP_009130.1, 220034_at
 Figure 2337: PRO20142
 Figure 2338: DNA328926, NP_064703.1, 220046_s_at
 Figure 2339: PRO84643
 Figure 2340A-B: DNA221079, NP_071445.1, 220066_at
 Figure 2341: PRO34753
 Figure 2342: DNA256091, NP_071385.1, 220094_s_at
 Figure 2343: PRO51141
 Figure 2344: DNA328927, NP_078993.2, 220122_at
 Figure 2345: PRO84644
 Figure 2346: DNA328928, NP_068377.1, 220178_at
 Figure 2347: PRO84645
 Figure 2348: DNA324716, NP_463459.1, 220189_s_at
 Figure 2349: PRO81347
 Figure 2350: DNA228059, NP_073742.1, 220199_s_at
 Figure 2351: PRO38522
 Figure 2352: DNA328929, NP_060375.1, 220240_s_at
 Figure 2353: PRO84646
 Figure 2354A-B: DNA328930, NP_038465.1, 220253_s_at
 Figure 2355: PRO23525
 Figure 2356: DNA328931, NP_004226.1, 220266_s_at
 Figure 2357: PRO84647
 Figure 2358: DNA328932, NP_079057.1, 220301_at
 Figure 2359: PRO84648
 Figure 2360: DNA328933, NP_057466.1, 220307_at
 Figure 2361: PRO9891
 Figure 2362: DNA256735, NP_060175.1, 220333_at
 Figure 2363: PRO51669
 Figure 2364A-B: DNA328934, EML4, 220386_s_at
 Figure 2365: PRO84649
 Figure 2366: DNA328935, NP_009002.1, 220387_s_at
 Figure 2367: PRO84650
 Figure 2368: DNA254861, MCOLN3, 220484_at
 Figure 2369: PRO49953
 Figure 2370: DNA328936, NP_066998.1, 220491_at
 Figure 2371: PRO1003
 Figure 2372: DNA328937, PHEMX, 220558_x_at
 Figure 2373: PRO12380
 Figure 2374: DNA328938, NP_060617.1, 220643_s_at
 Figure 2375: PRO84651
 Figure 2376: DNA323756, NP_057267.2, 220688_s_at
 Figure 2377: PRO80512
 Figure 2378: DNA328939, NP_008834.1, 220741_s_at
 Figure 2379: PRO84652
 Figure 2380: DNA288247, NP_478059.1, 220892_s_at
 Figure 2381: PRO70011
 Figure 2382: DNA328940, NP_078893.1, 220933_s_at
 Figure 2383: PRO84653
 Figure 2384: DNA328941, NP_055218.2, 220937_s_at
 Figure 2385: PRO84654
 Figure 2386: DNA327953, NP_055182.2, 220942_x_at
 Figure 2387: PRO83878
 Figure 2388A-B: DNA323882, NP_000692.2, 220948_s_at
 Figure 2389: PRO80625
 Figure 2390: DNA327917, NP_112240.1, 220966_x_at
 Figure 2391: PRO83852
 Figure 2392: DNA328942, NP_112216.2, 220985_s_at
 Figure 2393: PRO84655
 Figure 2394: DNA328943, NP_036566.1, 221041_s_at
 Figure 2395: PRO51680
 Figure 2396: DNA328944, NP_060554.1, 221078_s_at
 Figure 2397: PRO84656
 Figure 2398: DNA328945, NP_079177.2, 221081_s_at
 Figure 2399: PRO84657
 Figure 2400: DNA328946, NP_055164.1, 221087_s_at
 Figure 2401: PRO12343
 Figure 2402: DNA328947, NP_055245.1, 221188_s_at
 Figure 2403: PRO84658
 Figure 2404: DNA257293, NP_110396.1, 221210_s_at
 Figure 2405: PRO51888
 Figure 2406: DNA327920, NP_110431.1, 221245_s_at
 Figure 2407: PRO83855
 Figure 2408A-C: DNA328287, NP_072174.2, 221246_x_at
 Figure 2409: PRO84163
 Figure 2410: DNA328948, NP_110437.1, 221253_s_at
 Figure 2411: PRO84659
 Figure 2412: DNA256432, NP_110415.1, 221266_s_at
 Figure 2413: PRO51471
 Figure 2414: DNA328027, NP_112570.2, 221437_s_at
 Figure 2415: PRO83944
 Figure 2416A-B: DNA272014, AF084555, 221482_s_at
 Figure 2417: PRO60289
 Figure 2418: DNA328949, AF157510, 221487_s_at

Figure 2419: PRO84660
 Figure 2420: DNA328950, NP_057025.1, 221504_s_at
 Figure 2421: PRO84661
 Figure 2422A-B: DNA328951, HSM802232, 221523_s_at
 Figure 2423: PRO84662
 Figure 2424: DNA328952, NP_067067.1, 221524_s_at
 Figure 2425: PRO84663
 Figure 2426A-B: DNA273901, NP_110389.1, 221530_s_at
 Figure 2427: PRO61855
 Figure 2428: DNA274676, DKFZp564A176Homo, 221538_s_at
 Figure 2429: DNA328953, NP_004086.1, 221539_at
 Figure 2430: PRO70296
 Figure 2431A-B: DNA328954, NP_113664.1, 221541_at
 Figure 2432: PRO9851
 Figure 2433A-B: DNA269992, HUMACYLCOA, 221561_at
 Figure 2434: PRO58388
 Figure 2435: DNA328955, NP_054887.1, 221570_s_at
 Figure 2436: PRO84664
 Figure 2437A-B: DNA328956, AF110908, 221571_at
 Figure 2438: DNA188321, NP_004855.1, 221577_x_at
 Figure 2439: PRO21896
 Figure 2440: DNA328957, WBSCR5, 221581_s_at
 Figure 2441: PRO23859
 Figure 2442: DNA328958, BC001663, 221593_s_at
 Figure 2443: PRO84665
 Figure 2444: DNA328959, NP_077027.1, 221620_s_at
 Figure 2445: PRO4302
 Figure 2446: DNA254777, NP_055140.1, 221676_s_at
 Figure 2447: PRO49875
 Figure 2448: DNA327526, NP_065727.2, 221679_s_at
 Figure 2449: PRO83574
 Figure 2450: DNA328960, NP_076426.1, 221692_s_at
 Figure 2451: PRO84666
 Figure 2452: DNA327929, AK001785, 221748_s_at
 Figure 2453: PRO83861
 Figure 2454: DNA328961, NP_443112.1, 221756_at
 Figure 2455: PRO84667
 Figure 2456: DNA328962, BC021574, 221759_at
 Figure 2457: PRO82746
 Figure 2458A-B: DNA328963, 328765.9, 221760_at
 Figure 2459: PRO84668
 Figure 2460A-B: DNA327930, 1455324.9, 221765_at
 Figure 2461: PRO83862
 Figure 2462: DNA328964, AK056028, 221770_at
 Figure 2463: PRO84669
 Figure 2464A-C: DNA328965, AB051505, 221778_at
 Figure 2465A-B: DNA328966, BAB14908.1, 221790_s_at

Figure 2466: PRO84670
 Figure 2467: DNA328967, BC017905, 221815_at
 Figure 2468: PRO84671
 Figure 2469: DNA274058, NP_057203.1, 221816_s_at
 Figure 2470: PRO61999
 Figure 2471A-B: DNA328968, 1322249.6, 221830_at
 Figure 2472: PRO62511
 Figure 2473: DNA272419, AF105036, 221841_s_at
 Figure 2474: PRO60672
 Figure 2475: DNA299882, DNA299882, 221872_at
 Figure 2476: PRO70856
 Figure 2477: DNA328969, 334394.2, 221878_at
 Figure 2478: PRO84672
 Figure 2479: DNA327933, 1452741.11, 221899_at
 Figure 2480: PRO83865
 Figure 2481: DNA328970, NP_057696.1, 221920_s_at
 Figure 2482: PRO84673
 Figure 2483: DNA328971, AK000472, 221923_s_at
 Figure 2484: PRO84674
 Figure 2485: DNA254787, AK023140, 221935_s_at
 Figure 2486: PRO49885
 Figure 2487: DNA327114, NP_006004.1, 221989_at
 Figure 2488: PRO62466
 Figure 2489: DNA328972, BC009950, 222001_x_at
 Figure 2490: DNA328973, NP_115538.1, 222024_s_at
 Figure 2491: PRO82497
 Figure 2492: DNA119482, DNA119482, 222108_at
 Figure 2493: PRO9850
 Figure 2494: DNA328974, NP_061893.1, 222116_s_at
 Figure 2495: PRO84676
 Figure 2496: DNA287209, NP_056350.1, 222154_s_at
 Figure 2497: PRO69490
 Figure 2498: DNA328975, NP_078807.1, 222155_s_at
 Figure 2499: PRO47688
 Figure 2500: DNA328976, BC019091, 222206_s_at
 Figure 2501: PRO84677
 Figure 2502: DNA256784, NP_075069.1, 222209_s_at
 Figure 2503: PRO51716
 Figure 2504: DNA328977, NP_071344.1, 222216_s_at
 Figure 2505: PRO84678
 Figure 2506: DNA328978, NP_060373.1, 222244_s_at
 Figure 2507: PRO84679
 Figure 2508A-B: DNA328979, 006242.19, 222266_at
 Figure 2509: PRO84680
 Figure 2510: DNA328980, 7692031.1, 222273_at
 Figure 2511: PRO84681
 Figure 2512: DNA328981, AF443871, 222294_s_at
 Figure 2513: PRO24633
 Figure 2514: DNA328982, 154391.1, 222313_at
 Figure 2515: PRO84682
 Figure 2516: DNA328983, 206335.1, 222366_at
 Figure 2517: PRO84683

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTSI. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., *Prot. Eng.* 10:1-6 (1997) and von Heinje et al., *Nucl. Acids. Res.* 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length,

alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or 5 Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer 10 program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, 15 Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX 20 V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

25

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment 30 program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" 35 represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

40 However, % amino acid sequence identity values may also be obtained as described below by using the WU-

BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid

sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence

D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

5

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence 10 identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of 15 interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Most of 20 the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a 25 sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic 30 acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison 35 program NCBI-BLAST2 (Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, 40 constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

5

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in 10 D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

15 In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

20 "Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with 25 diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be 30 present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

35 An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polyepitopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a

solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length
5 and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody
10 does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin
15 constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any
20 immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-
25 occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully
30 blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic
35 molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those

in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time.

5 "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

10 Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of 15 physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating 20 agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (Zapata et al., *Protein Eng.* 8(10): 1057-1062 [1995]); single-chain 25 antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

30 "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and - binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising 35 only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge 40 region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains

bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their 5 constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

10 "Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

15 The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 20 20 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody 25 will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the 30 antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

35 The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can 40 adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass

(e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No.

5 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

10 A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

The term "immune related disease" means a disease in which a component of the immune system of a mammal causes, mediates or otherwise contributes to a morbidity in the mammal. Also included are diseases in which stimulation or intervention of the immune response has an ameliorative effect on progression of the disease. Included within this term are immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

15 The term "monocyte/macrophage mediated disease" means a disease in which monocytes/macrophages directly or indirectly mediate or otherwise contribute to a morbidity in a mammal. The monocyte/macrophage mediated disease may be associated with cell mediated effects, lymphokine mediated effects, *etc.*, and even effects associated with other immune cells if the cells are stimulated, for 20 example, by the lymphokines secreted by monocytes/macrophages.

25 Examples of immune-related and inflammatory diseases, some of which are immune mediated, which can be treated according to the invention include systemic lupus erythematosus, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune 30 thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating 35 polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin 40 diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft -versus-host-disease. Infectious diseases including viral diseases such as AIDS (HIV infection), hepatitis A, B, C, D, and E, herpes, *etc.*, bacterial infections, fungal infections, protozoal infections and parasitic infections.

5 The term "effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which results in achieving a particular stated purpose. An "effective amount" of a PRO polypeptide or agonist or antagonist thereof may be determined empirically. Furthermore, a "therapeutically effective amount" is a concentration or amount of a PRO polypeptide and/or agonist/antagonist which is effective for achieving a stated therapeutic effect. This amount may also be determined empirically.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., I¹³¹, I¹²⁵, Y⁹⁰ and Re¹⁸⁶), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

10 A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotapec, busulfan, cytoxin, taxoids, e.g., paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, 15 mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

20 A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such 25 as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 30 13.

30 The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming 35 growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); 40

osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL).

5 As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the 10 desired binding specificity which is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, 15 IgD or IgM.

Table 1

45

50

55

Table 1 (cont')

```

/*
*/
5  #include <stdio.h>
  #include <ctype.h>

#define MAXJMP 16      /* max jumps in a diag */
#define MAXGAP 24      /* don't continue to penalize gaps larger than this */
#define J MPS 1024     /* max jmps in an path */
10 #define MX 4        /* save if there's at least MX-1 bases since last jmp */

#define DMAT 3         /* value of matching bases */
#define DMIS 0         /* penalty for mismatched bases */
#define DINS0 8        /* penalty for a gap */
15 #define DINS1 1      /* penalty per base */
#define PINS0 8        /* penalty for a gap */
#define PINS1 4        /* penalty per residue */

20 struct jmp {
    short n[MAXJMP]; /* size of jmp (neg for delay) */
    unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
    }; /* limits seq to 2^16 -1 */

25 struct diag {
    int score; /* score at last jmp */
    long offset; /* offset of prev block */
    short ijmp; /* current jmp index */
    struct jmp jp; /* list of jmps */
    };
30 struct path {
    int spc; /* number of leading spaces */
    short n[J MPS]; /* size of jmp (gap) */
    int x[J MPS]; /* loc of jmp (last elem before gap) */
    };
35 };

40 char *ofile; /* output file name */
char *namex[2]; /* seq names: getseqs() */
char *prog; /* prog name for err msgs */
char *seqx[2]; /* seqs: getseqs() */
int dmax; /* best diag: nw() */
int dmax0; /* final diag */
int dna; /* set if dna: main() */
int endgaps; /* set if penalizing end gaps */
45 int gapx, gapy; /* total gaps in seqs */
int len0, len1; /* seq lens */
int ngapx, ngapy; /* total size of gaps */
int smax; /* max score: nw() */
int *xbm; /* bitmap for matching */
50 long offset; /* current offset in jmp file */
struct diag *dx; /* holds diagonals */
struct path pp[2]; /* holds path for seqs */

55 char *calloc(), *malloc(), *index(), *strcpy();
char *getseq(), *g_calloc();

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
5   * where file1 and file2 are two dna or two protein sequences.
 *   The sequences can be in upper- or lower-case an may contain ambiguity
 *   Any lines beginning with ';' or '>' are ignored
 *   Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *   A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10  * Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
20   1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
25   1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
   128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
   1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
   1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
30
  main
  int ac;
  char *av[ ];
{
  prog = av[0];
35  if (ac != 3) {
      fprintf(stderr, "usage: %s file1 file2\n", prog);
      fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
      fprintf(stderr, "The sequences can be in upper- or lower-case\n");
      fprintf(stderr, "Any lines beginning with ';' or '>' are ignored\n");
40  fprintf(stderr, "Output is in the file \"align.out\"\n");
      exit(1);
  }
  namex[0] = av[1];
  namex[1] = av[2];
45  seqx[0] = getseq(namex[0], &len0);
  seqx[1] = getseq(namex[1], &len1);
  xbm = (dna)? _dbval : _pbval;

50  endgaps = 0;           /* 1 to penalize endgaps */
  ofile = "align.out";    /* output file */

  nw();           /* fill in the matrix, get the possible jmps */
  readjmps();    /* get the actual jmps */
  print();        /* print stats, alignment */
55
  cleanup();      /* unlink any tmp files */
}

```

Table 1 (cont')

```

/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
5  * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw()
10   nw
11   {
12     char      *px, *py;      /* seqs and ptrs */
13     int       *ndely, *dely;  /* keep track of dely */
14     int       ndelx, delx;  /* keep track of delx */
15     int       *tmp;        /* for swapping row0, row1 */
16     int       mis;        /* score for each type */
17     int       ins0, ins1;  /* insertion penalties */
18     register id;        /* diagonal index */
19     register ij;        /* jmp index */
20     register *col0, *col1; /* score for curr, last row */
21     register xx, yy;    /* index into seqs */

22     dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

23     ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
24     dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
25     col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
26     col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
27     ins0 = (dna)? DINS0 : PINS0;
28     ins1 = (dna)? DINS1 : PINS1;

29     smax = -10000;
30     if (endgaps) {
31       for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
32         col0[yy] = dely[yy] = col0[yy-1] - ins1;
33         ndely[yy] = yy;
34       }
35       col0[0] = 0;      /* Waterman Bull Math Biol 84 */
36     }
37     else
38       for (yy = 1; yy <= len1; yy++)
39         dely[yy] = -ins0;

40     /* fill in match matrix
41     */
42     for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
43       /* initialize first entry in col
44       */
45       if (endgaps) {
46         if (xx == 1)
47           col1[0] = delx = -(ins0+ins1);
48         else
49           col1[0] = delx = col0[0] - ins1;
50         ndelx = xx;
51       }
52       else {
53         col1[0] = 0;
54         delx = -ins0;
55         ndelx = 0;
56       }
57     }
58   }
59 }
```

Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }
}

/* update penalty for del in y seq;
 * favor new del over ongong del
 */
if (endgaps || ndelx < MAXGAP) {
    if (col1[yy-1] - ins0 >= delx) {
        delx = col1[yy-1] - (ins0+ins1);
        ndelx = 1;
    } else {
        delx -= ins1;
        ndelx++;
    }
} else {
    if (col1[yy-1] - (ins0+ins1) >= delx) {
        delx = col1[yy-1] - (ins0+ins1);
        ndelx = 1;
    } else
        ndelx++;
}

/* pick the maximum score; we're favoring
 * mis over any del and delx over dely
 */

```

55

60

Table 1 (cont')

...nw

```

5      id = xx - yy + len1 - 1;
      if (mis >= delx && mis >= dely[yy])
          col1[yy] = mis;
      else if (delx >= dely[yy]) {
          col1[yy] = delx;
          ij = dx[id].ijmp;
          if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
              dx[id].ijmp++;
              if (++ij >= MAXJMP) {
                  writejmps(id);
                  ij = dx[id].ijmp = 0;
                  dx[id].offset = offset;
                  offset += sizeof(struct jmp) + sizeof(offset);
              }
          }
          dx[id].jp.n[ij] = ndelx;
          dx[id].jp.x[ij] = xx;
          dx[id].score = delx;
      }
      else {
          col1[yy] = dely[yy];
          ij = dx[id].ijmp;
20      if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
              && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                  dx[id].ijmp++;
                  if (++ij >= MAXJMP) {
                      writejmps(id);
                      ij = dx[id].ijmp = 0;
                      dx[id].offset = offset;
                      offset += sizeof(struct jmp) + sizeof(offset);
                  }
              }
          }
          dx[id].jp.n[ij] = -ndely[yy];
          dx[id].jp.x[ij] = xx;
          dx[id].score = dely[yy];
      }
      if (xx == len0 && yy < len1) {
          /* last col
          */
          if (endgaps)
              col1[yy] -= ins0+ins1*(len1-yy);
40      if (col1[yy] > smax) {
                  smax = col1[yy];
                  dmax = id;
              }
          }
          if (endgaps && xx < len0)
              col1[yy-1] -= ins0+ins1*(len0-xx);
          if (col1[yy-1] > smax) {
50      smax = col1[yy-1];
                  dmax = id;
              }
          }
          tmp = col0; col0 = col1; col1 = tmp;
      }
      (void) free((char *)ndely);
      (void) free((char *)dely);
      (void) free((char *)col0);
      (void) free((char *)col1);
  }

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
 * static:
 *  getmat() -- trace back best path, count matches: print()
 *  pr_align() -- print alignment of described in array p[ ]; print()
 *  dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 *  nums() -- put out a number line: dumpblock()
 *  putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 *  stars() -- put a line of stars: dumpblock()
 *  stripname() -- strip any path and prefix from a seqname
 */
15
#include "nw.h"

#define SPC      3
#define P_LINE   256      /* maximum output line */
20 #define P_SPC   3      /* space between name or num and seq */

extern  _day[26][26];
int    olen;           /* set output line length */
FILE   *fx;            /* output file */
25

print()
{
    print
    {
        int     lx, ly, firstgap, lastgap;      /* overlap */

30    if ((fx = fopen(ofile, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, ofile);
            cleanup(1);
        }
35    fprintf(fx, "< first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
40    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
45    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
50    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
55    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}
60

```

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
5 static
getmat(lx, ly, firstgap, lastgap)                                getmat
    int      lx, ly;                                              /* "core" (minus endgaps) */
    int      firstgap, lastgap;                                     /* leading/trailing overlap */
{
10    int      nm, i0, i1, siz0, siz1;
    char     outx[32];
    double   pct;
    register int n0, n1;
    register char *p0, *p1;
15
    /* get total matches, score
     */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
20    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;
25
    nm = 0;
    while (*p0 && *p1) {
        if (siz0) {
30            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
            p0++;
            n0++;
            siz1--;
        }
        else {
35            if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].n[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].n[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
45
        }
    }
50
    /* pct homology:
     * if penalizing endgaps, base is the shorter seq
     * else, knock off overhangs and take shorter core
     */
    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
55        lx = (lx < ly)? lx : ly;
    pct = 100.* (double)nm/(double)lx;
    fprintf(fx, "\n");
    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
60        nm, (nm == 1)? "" : "es", lx, pct);

```

Table 1 (cont')

```

5      fprintf(fx, "<gaps in first sequence: %d", gapx);
...getmat
if (gapx) {
  (void) sprintf(outx, " (%d %s%s)",
    ngapx, (dna)? "base":"residue", (ngapx == 1)? ":"s");
  fprintf(fx, "%s", outx);

10     fprintf(fx, ", gaps in second sequence: %d", gapy);
if (gapy) {
  (void) sprintf(outx, " (%d %s%s)",
    ngapy, (dna)? "base":"residue", (ngapy == 1)? ":"s");
  fprintf(fx, "%s", outx);
15   }
if (dna)
  fprintf(fx,
  "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
  smax, DMAT, DMIS, DINS0, DINS1);
20   else
  fprintf(fx,
  "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
  smax, PINS0, PINS1);
if (endgaps)
  fprintf(fx,
  "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
  firstgap, (dna)? "base" : "residue", (firstgap == 1)? ":"s",
  lastgap, (dna)? "base" : "residue", (lastgap == 1)? ":"s");
25   else
  fprintf(fx, "<endgaps not penalized\n");
30 }
static nm;          /* matches in core -- for checking */
static lmax;        /* lengths of stripped file names */
static ij[2];        /* jmp index for a path */
35 static nc[2];        /* number at start of current line */
static ni[2];        /* current elem number -- for gapping */
static siz[2];
static char *ps[2];    /* ptr to current element */
static char *po[2];    /* ptr to next output char slot */
40 static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */

/*
* print alignment of described in struct path pp[ ]
45 */
static
pr_align()
  pr_align
{
50   int nn;          /* char count */
   int more;
   register i;

    for (i = 0, lmax = 0; i < 2; i++) {
      nn = stripname(namex[i]);
      if (nn > lmax)
        lmax = nn;

55   nc[i] = 1;
   ni[i] = 1;
   siz[i] = ij[i] = 0;
   ps[i] = seqx[i];
   po[i] = out[i];
60   }
}

```

Table 1 (cont')

```

for (nn = nm = 0, more = 1; more; ) {
    ...pr_align
        for (i = more = 0; i < 2; i++) {
            /*
             * do we have more of this sequence?
             */
            if (!*ps[i])
                continue;
            more++;

            if (pp[i].spc) { /* leading space */
                *po[i]++ = ' ';
                pp[i].spc--;
            }
            else if (siz[i]) { /* in a gap */
                *po[i]++ = '-';
                siz[i]--;
            }
            else { /* we're putting a seq element
                    */
                *po[i] = *ps[i];
                if (islower(*ps[i]))
                    *ps[i] = toupper(*ps[i]);
                po[i]++;
                ps[i]++;
            }
            /*
             * are we at next gap for this seq?
             */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                 * we need to merge all gaps
                 * at this location
                 */
                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]++];
            }
            ni[i]++;
        }
    }
    if (++nn == olen || !more && nn) {
        dumpblock();
        for (i = 0; i < 2; i++)
            po[i] = out[i];
        nn = 0;
    }
}
/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
static
dumpblock()
{
    register i;
    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
}

```

Table 1 (cont')

```

...dumpblock

5   (void) putc('\n', fx);
  for (i = 0; i < 2; i++) {
    if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
      if (i == 0)
        nums(i);
      if (i == 0 && *out[1])
        stars();
      putline(i);
      if (i == 0 && *out[1])
        fprintf(fx, star);
      if (i == 1)
        nums(i);
15
    }
  }

20  /*
 * put out a number line: dumpblock()
 */
static
  nums(ix)                                nums
25  int      ix;      /* index in out[ ] holding seq line */
{
  char      nline[P_LINE];
  register  i, j;
  register char  *pn, *px, *py;
30
  for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
    *pn = ' ';
  for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
    if (*py == ' ' || *py == '-')
      *pn = ' ';
    else {
      if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
        j = (i < 0)? -i : i;
        for (px = pn; j /= 10, px--)
          *px = j%10 + '0';
        if (i < 0)
          *px = '-';
      }
      else
        *pn = ' ';
      i++;
    }
  }
50  *pn = '\0';
  nc[ix] = i;
  for (pn = nline; *pn; pn++)
    (void) putc(*pn, fx);
  (void) putc('\n', fx);
}
55
/*
 * put out a line (name, [num], seq, [num]): dumpblock()
 */
static
  putline(ix)                                putline
60  int      ix;      {

```

Table 1 (cont')

```

...putline
5      int          i;
      register char *px;

10     for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
           (void) putc(*px, fx);
      for (; i < lmax+P_SPC; i++)
           (void) putc(' ', fx);

15     /* these count from 1:
      * ni[ ] is current element (from 1)
      * nc[ ] is number at start of current line
      */
      for (px = out[ix]; *px; px++)
           (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
20     }

25     /*
      * put a line of stars (seqs always in out[0], out[1]): dumpblock()
      */
25     static
stars() {
      stars
      {
30     int          i;
      register char *p0, *p1, cx, *px;

35     if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
           !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
           return;
      px = star;
      for (i = lmax+P_SPC; i; i--)
           *px++ = ' ';

40     for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
           if (isalpha(*p0) && isalpha(*p1)) {

45           if (xbm[*p0-'A']&xbm[*p1-'A']) {
               cx = '*';
               nm++;
               }
           else if (!dma && _day[*p0-'A'][*p1-'A'] > 0)
               cx = '.';
           else
               cx = ' ';
50           }
           else
               cx = ' ';
           *px++ = cx;
           }
55     *px++ = '\n';
     *px = '\0';
     }
}

```

Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
5  static
  stripname(pn)
    stripname
      char      *pn;      /* file name (may be path) */
10   {
      register char    *px, *py;

      py = 0;
      for (px = pn; *px; px++)
        if (*px == '/')
15        py = px + 1;
      if (py)
        (void) strcpy(pn, py);
      return(strlen(pn));
20  }
```

25

30

35

40

45

50

55

60

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
5   #include "nw.h"
10  #include <sys/file.h>

    char *jname = "/tmp/homgXXXXXX";           /* tmp file for jmps */
    FILE *fj;

15  int cleanup();                         /* cleanup tmp file */
    long lseek();

    /*
     * remove any tmp file if we blow
     */
20
    cleanup(i)
        int i;
    {
        if (fj)
            (void) unlink(jname);
        exit(i);
    }

    /*
30   * read, return ptr to seq, set dna, len, maxlen
     * skip lines starting with ';', '<', or '>'
     * seq in upper or lower case
     */
    char *
35   getseq(file, len)                      getseq
        char *file; /* file name */
        int *len; /* seq len */
    {
        char line[1024], *pseq;
40   register char *px, *py;
        int natgc, tlen;
        FILE *fp;

        if ((fp = fopen(file, "r")) == 0) {
            fprintf(stderr, "%s: can't read %s\n", prog, file);
            exit(1);
        }
        tlen = natgc = 0;
50   while (fgets(line, 1024, fp)) {
            if (*line == ';' || *line == '<' || *line == '>')
                continue;
            for (px = line; *px != '\n'; px++)
                if (isupper(*px) || islower(*px))
                    tlen++;
        }
55   if ((pseq = malloc((unsigned)(tlen+6))) == 0)
            fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
60   pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

Table 1 (cont')

```

    ...getseq
5      py = pseq + 4;
      *len = tlen;
      rewind(fp);

10     while (fgets(line, 1024, fp)) {
          if (*line == ';' || *line == '<' || *line == '>')
              continue;
          for (px = line; *px != '\n'; px++) {
              if (isupper(*px))
                  *py++ = *px;
              else if (islower(*px))
                  *py++ = toupper(*px);
              if (index("ATGCU", *(py-1)))
                  natgc++;
          }
      }
      *py++ = '\0';
      *py = '\0';
      (void) fclose(fp);
      dna = natgc > (tlen/3);
      return(pseq+4);
25
20
25     char *
30     g_malloc(msg, nx, sz)
35     {
40         char *msg; /* program, calling routine */
         int nx, sz; /* number and size of elements */
45         char *px, *calloc();
50
55         if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
          if (*msg) {
              fprintf(stderr, "%s: g_malloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
              exit(1);
          }
        }
40     }
45
40
45     readjmps()
50
55     readjmps()
55     {
60         int fd = -1;
         int siz, i0, i1;
         register i, j, xx;
65
65         if (fj) {
              (void) fclose(fj);
              if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                  fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                  cleanup(1);
              }
            }
60         for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
              while (1) {
                  for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                      ;
              }
            }
        }

```

Table 1 (cont')**...readjmps**

```

5           if (j < 0 && dx[dmax].offset && fj) {
                  (void) lseek(fd, dx[dmax].offset, 0);
                  (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
                  (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
                  dx[dmax].ijmp = MAXJMP-1;
}
10          else
                  break;
}
15          if (i >= JMPS) {
                  fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                  cleanup(1);
}
16          if (j >= 0) {
                  siz = dx[dmax].jp.n[j];
                  xx = dx[dmax].jp.x[j];
                  dmax += siz;
20          if (siz < 0) { /* gap in second seq */
                  pp[1].n[i1] = -siz;
                  xx += siz;
                  /* id = xx - yy + len1 - 1
                  */
25          pp[1].x[i1] = xx - dmax + len1 - 1;
                  gapy++;
                  ngapy -= siz;
}
26          /* ignore MAXGAP when doing endgaps */
                  siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
30          i1++;
}
35          else if (siz > 0) { /* gap in first seq */
                  pp[0].n[i0] = siz;
                  pp[0].x[i0] = xx;
                  gapx++;
                  ngapx += siz;
}
36          /* ignore MAXGAP when doing endgaps */
                  siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
37          i0++;
40          }
}
45          else
                  break;
}
46          /* reverse the order of jmps
 */
50          for (j = 0, i0--; j < i0; j++, i0--) {
                  i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
                  i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
}
55          for (j = 0, i1--; j < i1; j++, i1--) {
                  i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
                  i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
}
56          if (fd >= 0)
                  (void) close(fd);
60          if (fj) {
                  (void) unlink(jname);
                  fj = 0;
                  offset = 0;
}

```

Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5   writejmps(ix)
    writejmps
    int      ix;
10  {
    char    *mktemp();

    if (!fj) {
        if (mktemp(jname) < 0) {
            fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
            cleanup(1);
15        }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
20        }
    }
    (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
25
}

```

Table 2

5 PRO XXXXXXXXXXXXXXXXX (Length = 15 amino acids)
 Comparison Protein XXXXXYYYYYYY (Length = 12 amino acids)
 % amino acid sequence identity =
 (the number of identically matching amino acid residues between the two polypeptide sequences as
 10 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 15 = 33.3%

Table 3

15 PRO XXXXXXXXXX (Length = 10 amino acids)
 Comparison Protein XXXXXYYYYYYZZYZ (Length = 15 amino acids)
 % amino acid sequence identity =
 (the number of identically matching amino acid residues between the two polypeptide sequences as
 20 determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
 5 divided by 10 = 50%

Table 4

25	PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
	Comparison DNA	NNNNNNLLLLLLLL	(Length = 16 nucleotides)
% nucleic acid sequence identity =			
30	(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) = 6 divided by 14 = 42.9%		

Table 5

35	PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
	Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

5 4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding 10 polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their 15 origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been disclosed. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

20 B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of 25 the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a 30 substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally, the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of 35 homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally

be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR.

Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	Original Residue	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
10	Cys (C)	ser	ser
	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
15	Ile (I)	leu; val; met; ala; phe; norleucine	leu
	Leu (L)	norleucine; ile; val; met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
20	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
25	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe; ala; norleucine	leu

30 Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

35 (1) hydrophobic: norleucine, met, ala, val, leu, ile;
 (2) neutral hydrophilic: cys, ser, thr;
 (3) acidic: asp, glu;
 (4) basic: asn, gln, his, lys, arg;
 (5) residues that influence chain orientation: gly, pro; and
 40 (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated 45 (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., *Nucl. Acids Res.*, 13:4331 (1986); Zoller et al., *Nucl. Acids Res.*, 10:6487 (1987)], cassette mutagenesis [Wells et al., *Gene*, 34:315 (1985)], restriction selection mutagenesis [Wells et al., *Philos.*

Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by,

one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

5 Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

10 Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

15 Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

20 The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

25 In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an alpha-tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

30 In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric

5 molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or 10 the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO

10 The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using 15 manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

1. Isolation of DNA Encoding PRO

20 DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

25 Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold 30 Spring Harbor Laboratory Press, 1995)].

35 The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence

databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or 5 genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

10 2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing 15 promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., *supra*.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending 20 on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., *supra*, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation 25 method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfactions have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other 30 methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as 35 Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*,

Erwinia, Klebsiella, Proteus, Salmonella, e.g., *Salmonella typhimurium, Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly 5 preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 10 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, 15 e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, *Nature*, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 20 4,943,529; Fleer et al., *Bio/Technology*, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., *J. Bacteriol.*, 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., *Bio/Technology*, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., *J. Basic Microbiol.*, 25 28:265-278 [1988]); *Candida*; *Trichoderma reesiae* (EP 244,234); *Neurospora crassa* (Case et al., *Proc. Natl. Acad. Sci. USA*, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., *Biochem. Biophys. Res. Commun.*, 112:284-289 [1983]; Tilburn et al., *Gene*, 26:205-30 221 [1983]; Yelton et al., *Proc. Natl. Acad. Sci. USA*, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, *EMBO J.*, 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, *The Biochemistry of Methylotrophs*, 35 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila S2* and *Spodoptera Sf9*, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary

(CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen. Virol.*, 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77:4216 (1980)); mouse sertoli cells (TM4, 5 Mather, *Biol. Reprod.*, 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. 10 The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. 15 Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific 20 cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion 25 the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

30 Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

35 Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c)

supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (trp) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to

300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer 5 on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the 10 termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in 15 recombinant vertebrate cell culture are described in Gething et al., *Nature*, 293:620-625 (1981); Mantei et al., *Nature*, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, *Proc. 20 Natl. Acad. Sci. USA*, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, 25 the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any 30 mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or 35 chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

5 E. Tissue Distribution

The location of tissues expressing the PRO can be identified by determining mRNA expression in various human tissues. The location of such genes provides information about which tissues are most likely to be affected by the stimulating and inhibiting activities of the PRO polypeptides. The location of 15 a gene in a specific tissue also provides sample tissue for the activity blocking assays discussed below.

As noted before, gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 [1980]), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled 20 probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to 25 quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence of a PRO polypeptide or against a synthetic peptide based on the DNA sequences encoding the PRO polypeptide or against an 30 exogenous sequence fused to a DNA encoding a PRO polypeptide and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for Northern blotting and *in situ* hybridization are provided below.

35 F. Antibody Binding Studies

The activity of the PRO polypeptides can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides, respectively, on tissue cells is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and 35 heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, *Monoclonal Antibodies: A Manual of Techniques*, pp.147-158 (CRC Press, Inc., 1987).

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are 5 insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody which is immobilized on a solid support, and thereafter a second 10 antibody binds to the analyte, thus forming an insoluble three-part complex. See, e.g., US Pat No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

15 For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

G. Cell-Based Assays

Cell-based assays and animal models for immune related diseases can be used to further understand the relationship between the genes and polypeptides identified herein and the development and 20 pathogenesis of immune related disease.

In a different approach, cells of a cell type known to be involved in a particular immune related disease are transfected with the cDNAs described herein, and the ability of these cDNAs to stimulate or inhibit immune function is analyzed. Suitable cells can be transfected with the desired gene, and monitored for immune function activity. Such transfected cell lines can then be used to test the ability of 25 poly- or monoclonal antibodies or antibody compositions to inhibit or stimulate immune function, for example to modulate monocyte/macrophage proliferation or inflammatory cell infiltration. Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of immune related diseases.

In addition, primary cultures derived from transgenic animals (as described below) can be used in 30 the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art (see, e.g., Small *et al.*, *Mol. Cell. Biol.* 5: 642-648 [1985]).

The use of an agonist stimulating compound has also been validated experimentally. Activation of 4-1BB by treatment with an agonist anti-4-1BB antibody enhances eradication of tumors. Hellstrom, I. 35 and Hellstrom, K. E., *Crit. Rev. Immunol.* (1998) 18:1. Immunoadjuvant therapy for treatment of tumors, described in more detail below, is another example of the use of the stimulating compounds of the invention.

Alternatively, an immune stimulating or enhancing effect can also be achieved by administration of a PRO which has vascular permeability enhancing properties. Enhanced vascular permeability would be beneficial to disorders which can be attenuated by local infiltration of immune cells (*e.g.*, monocytes/macrophages, eosinophils, PMNs) and inflammation.

5 On the other hand, PRO polypeptides, as well as other compounds of the invention, which are direct inhibitors of monocyte/macrophage proliferation/activation, lymphokine secretion, and/or vascular permeability can be directly used to suppress the immune response. These compounds are useful to reduce the degree of the immune response and to treat immune related diseases characterized by a hyperactive, superoptimal, or autoimmune response. The use of compound which suppress vascular
10 permeability would be expected to reduce inflammation. Such uses would be beneficial in treating conditions associated with excessive inflammation.

15 Alternatively, compounds, *e.g.*, antibodies, which bind to stimulating PRO polypeptides and block the stimulating effect of these molecules produce a net inhibitory effect and can be used to suppress the monocyte/macrophage mediated immune response by inhibiting monocyte/macrophage proliferation/activation and/or lymphokine secretion. Blocking the stimulating effect of the polypeptides suppresses the immune response of the mammal.

H. Animal Models

20 The results of the cell based *in vitro* assays can be further verified using *in vivo* animal models and assays for monocyte/macrophage function. A variety of well known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of immune related disease, and to test the efficacy of candidate therapeutic agents, including antibodies, and other antagonists of the native polypeptides, including small molecule antagonists. The *in vivo* nature of such models makes them predictive of responses in human patients. Animal models of immune related diseases include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models
25 include, for example, rodent, *e.g.*, murine models. Such models can be generated by introducing cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, *etc.*

30 Graft-versus-host disease occurs when immunocompetent cells are transplanted into immunosuppressed or tolerant patients. The donor cells recognize and respond to host antigens. The response can vary from life threatening severe inflammation to mild cases of diarrhea and weight loss. Graft-versus-host disease models provide a means of assessing monocyte/macrophage reactivity against MHC antigens and minor transplant antigens. A suitable procedure is described in detail in Current Protocols in Immunology, above, unit 4.3.

35 Animal models for delayed type hypersensitivity provides an assay of cell mediated immune function as well. In chronic Delayed type hypersensitivity (DTH) reactions, monocytes that have differentiated into macrophages lead to the destruction of host tissue which is replaced by fibrous tissue (fibrosis).

Contact hypersensitivity is a simple delayed type hypersensitivity *in vivo* assay of cell mediated immune function. In this procedure, cutaneous exposure to exogenous haptens which gives rise to a delayed type hypersensitivity reaction which is measured and quantitated. Contact sensitivity involves an initial sensitizing phase followed by an elicitation phase. The elicitation phase occurs when the T 5 lymphocytes encounter an antigen to which they have had previous contact. Swelling and inflammation occur, making this an excellent model of human allergic contact dermatitis. At this point, monocytes leave the blood and differentiate into macrophages. A suitable procedure is described in detail in *Current Protocols in Immunology*, Eds. J. E. Cologan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, John Wiley & Sons, Inc., 1994, unit 4.2. See also Grabbe, S. and Schwarz, T, *Immun. 10 Today* 19 (1): 37-44 (1998)

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, 15 chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (Hoppe and Wanger, U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci. USA* 82, 6148-615 [1985]); gene targeting in embryonic stem cells (Thompson *et al.*, *Cell* 56, 313-321 [1989]); electroporation of embryos (Lo, *Mol. Cel. Biol.* 3, 1803-1814 [1983]); sperm-mediated gene transfer 20 (Lavitrano *et al.*, *Cell* 57, 717-73 [1989]). For review, see, for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, *Proc. Natl. 25 Acad. Sci. USA* 89, 6232-636 (1992).

The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry.

30 The animals may be further examined for signs of immune disease pathology, for example by histological examination to determine infiltration of immune cells into specific tissues. Blocking experiments can also be performed in which the transgenic animals are treated with the compounds of the invention to determine the extent of the monocyte/macrophage proliferation stimulation or inhibition of the compounds. In these experiments, blocking antibodies which bind to the PRO polypeptide, prepared 35 as described above, are administered to the animal and the effect on immune function is determined.

Alternatively, "knock out" animals can be constructed which have a defective or altered gene encoding a polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the polypeptide and altered genomic DNA encoding the same polypeptide introduced into

an embryonic cell of the animal. For example, cDNA encoding a particular polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several 5 kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li *et al.*, *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or 10 rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to 15 create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the polypeptide.

I. ImmunoAdjuvant Therapy

In one embodiment, the immunostimulating compounds of the invention can be used in 20 immunoadjuvant therapy for the treatment of tumors (cancer). It is now well established that monocytes/macrophages recognize human tumor specific antigens. One group of tumor antigens, encoded by the MAGE, BAGE and GAGE families of genes, are silent in all adult normal tissues, but are expressed in significant amounts in tumors, such as melanomas, lung tumors, head and neck tumors, and bladder carcinomas. DeSmet, C. *et al.*, (1996) *Proc. Natl. Acad. Sci. USA*, 93:7149. It has been shown 25 that stimulation of immune cells induces tumor regression and an antitumor response both *in vitro* and *in vivo*. Melero, I. *et al.*, *Nature Medicine* (1997) 3:682; Kwon, E. D. *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94: 8099; Lynch, D. H. *et al.*, *Nature Medicine* (1997) 3:625; Finn, O. J. and Lotze, M. T., *J. Immunol.* (1998) 21:114. The stimulatory compounds of the invention can be administered as adjuvants, alone or together with a growth regulating agent, cytotoxic agent or chemotherapeutic agent, to stimulate 30 monocyte/macrophage proliferation/activation and an antitumor response to tumor antigens. The growth regulating, cytotoxic, or chemotherapeutic agent may be administered in conventional amounts using known administration regimes. Immunostimulating activity by the compounds of the invention allows reduced amounts of the growth regulating, cytotoxic, or chemotherapeutic agents thereby potentially lowering the toxicity to the patient.

35 J. Screening Assays for Drug Candidates

Screening assays for drug candidates are designed to identify compounds that bind to or complex with the polypeptides encoded by the genes identified herein or a biologically active fragment thereof, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such

screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds, including peptides, preferably soluble peptides, (poly)peptide-immunoglobulin fusions, and, in particular, antibodies including, without limitation, poly-
5 and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art. All assays are common in that they call for contacting the drug candidate with a polypeptide encoded
10 by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent
15 attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When
20 the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labelled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular protein encoded by a gene identified herein, its interaction with that protein can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields
25 and co-workers [Fields and Song, *Nature (London)* 340, 245-246 (1989); Chien *et al.*, *Proc. Natl. Acad. Sci. USA* 88, 9578-9582 (1991)] as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89, 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, while the other one functioning as the transcription activation domain. The yeast expression system described in the foregoing publications
30 (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-lacZ reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4
35

activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKERTM) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific 5 protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

In order to find compounds that interfere with the interaction of a gene identified herein and other intra- or extracellular components can be tested, a reaction mixture is usually prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a test compound to inhibit binding, 10 the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described above. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test 15 compound and its reaction partner.

K. Compositions and Methods for the Treatment of Immune Related Diseases

The compositions useful in the treatment of immune related diseases include, without limitation, 20 proteins, antibodies, small organic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple helix molecules, *etc.* that inhibit or stimulate immune function, for example, monocyte proliferation/activation, lymphokine release, or immune cell infiltration.

For example, antisense RNA and RNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.*, between about -10 and +10 25 positions of the target gene nucleotide sequence, are preferred.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified 30 by known techniques. For further details see, *e.g.*, Rossi, *Current Biology* 4, 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, *e.g.*, PCT 35 publication No. WO 97/33551, *supra*.

These molecules can be identified by any or any combination of the screening assays discussed above and/or by any other screening techniques well known for those skilled in the art.

5 L. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

10 5 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

15 15 2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 20 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. 25 Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, (1986) 30 pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The 35 hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained,

for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

5 The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).
10 Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

15 After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

20 The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

25 The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).
30 The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

35 The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region

so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

5 3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding 10 subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by 15 corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The 20 humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are 25 typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such 30 "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

35 Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy,

Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

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4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered

from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan).

5 Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

10 Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) 15 derivatives. One of the Fab' -TNB derivatives is then reconverted to the Fab' -thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab' -TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

20 Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

25 Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then 30 re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain 35 variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a 5 triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (Fc γ R), such as Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These 10 antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been 15 proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and 20 methyl-4-mercaptopbutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) 25 may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, *J. Exp Med.*, 176: 1191-1195 (1992) and Shopes, *J. Immunol.*, 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as 30 described in Wolff *et al.* *Cancer Research*, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, *Anti-Cancer Drug Design*, 3: 219-230 (1989).

7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a 35 cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain,

nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the 5 tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁹⁰Y, and ¹⁸⁶Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as 10 disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis-(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of 15 radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then 20 administration of a "ligand" (e.g., avidin) that is conjugated to a cytotoxic agent (e.g., a radionucleotide).

8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, *Proc. Natl. Acad. Sci. USA*, 82: 3688 (1985); Hwang *et al.*, *Proc. Natl. Acad. Sci. USA*, 77: 4030 25 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized 30 phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, *J. Biol. Chem.*, 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, *J. National Cancer Inst.*, 81(19): 1484 (1989).

35 M. Pharmaceutical Compositions

The active PRO molecules of the invention (e.g., PRO polypeptides, anti-PRO antibodies, and/or variants of each) as well as other molecules identified by the screening assays disclosed above, can be administered for the treatment of immune related diseases, in the form of pharmaceutical compositions.

Therapeutic formulations of the active PRO molecule, preferably a polypeptide or antibody of the invention, are prepared for storage by mixing the active molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions.

5 Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-10 cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., 15 Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Compounds identified by the screening assays disclosed herein can be formulated in an analogous manner, using standard techniques well known in the art.

20 Lipofections or liposomes can also be used to deliver the PRO molecule into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology (see, e.g., Marasco *et al.*, *Proc. Natl. Acad. Sci. USA* 90, 7889-7893 [1993]).

25 The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

30 The active PRO molecules may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

35 The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations or the PRO molecules may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ -ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymer such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

N. Methods of Treatment

It is contemplated that the polypeptides, antibodies and other active compounds of the present invention may be used to treat various immune related diseases and conditions, such as 20 monocyte/macrophage diseases, including those characterized by infiltration of inflammatory cells into a tissue, stimulation of monocyte/macrophages, inhibition of monocytes/macrophages, increased or decreased vascular permeability or the inhibition thereof.

Exemplary conditions or disorders to be treated with the polypeptides, antibodies and other compounds of the invention, include, but are not limited to systemic lupus erythematosus, rheumatoid 25 arthritis, juvenile chronic arthritis, osteoarthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, 30 atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary 35 cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis, allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and

urticaria, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis, transplantation associated diseases including graft rejection and graft - versus-host-disease.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that mainly involves the synovial membrane of multiple joints with resultant injury to the articular cartilage. The pathogenesis is T lymphocyte dependent and is associated with the production of rheumatoid factors, auto-antibodies directed against self IgG, with the resultant formation of immune complexes that attain high levels in joint fluid and blood. These complexes in the joint may induce the marked infiltrate of lymphocytes and monocytes/macrophages into the synovium and subsequent marked synovial changes; the joint space/fluid if infiltrated by similar cells with the addition of numerous neutrophils. Tissues affected are primarily the joints, often in symmetrical pattern. However, extra-articular disease also occurs in two major forms. One form is the development of extra-articular lesions with ongoing progressive joint disease and typical lesions of pulmonary fibrosis, vasculitis, and cutaneous ulcers. The second form of extra-articular disease is the so called Felty's syndrome which occurs late in the RA disease course, sometimes after joint disease has become quiescent, and involves the presence of neutropenia, thrombocytopenia and splenomegaly. This can be accompanied by vasculitis in multiple organs with formations of infarcts, skin ulcers and gangrene. Patients often also develop rheumatoid nodules in the subcutis tissue overlying affected joints; the nodules late stage have necrotic centers surrounded by a mixed inflammatory cell infiltrate. Other manifestations which can occur in RA include: pericarditis, pleuritis, coronary arteritis, intestinal pneumonitis with pulmonary fibrosis, keratoconjunctivitis sicca, and rheumatoid nodules. The number and activation state of macrophages in the inflamed synovius correlates with the significance of RA (Kinne et al., 2000 Arthritis Res. 2: 189-202). As described above, macrophages are not believed to be involved in the early events of RA, but monocytes/macrophages have tissue destructive and tissue remodeling properties which may contribute to both acute and chronic RA.

Juvenile chronic arthritis is a chronic idiopathic inflammatory disease which begins often at less than 16 years of age. Its phenotype has some similarities to RA; some patients which are rheumatoid factor positive are classified as juvenile rheumatoid arthritis. The disease is sub-classified into three major categories: pauciarticular, polyarticular, and systemic. The arthritis can be severe and is typically destructive and leads to joint ankylosis and retarded growth. Other manifestations can include chronic anterior uveitis and systemic amyloidosis.

Spondyloarthropathies are a group of disorders with some common clinical features and the common association with the expression of HLA-B27 gene product. The disorders include: ankylosing spondylitis, Reiter's syndrome (reactive arthritis), arthritis associated with inflammatory bowel disease, spondylitis associated with psoriasis, juvenile onset spondyloarthropathy and undifferentiated spondyloarthropathy. Distinguishing features include sacroileitis with or without spondylitis; inflammatory asymmetric arthritis; association with HLA-B27 (a serologically defined allele of the HLA-B locus of class I MHC); ocular inflammation, and absence of autoantibodies associated with other rheumatoid disease. It was shown that CD163+ macrophages were increased in the synovial lining and

colonic mucosa in Spondyloarthropathy and correlates with the expression of HLA-DR and the production of TNF-alpha (Baeten et al., 2002 J Pathol 196(3):343-350).

Systemic sclerosis (scleroderma) has an unknown etiology. A hallmark of the disease is induration of the skin; likely this is induced by an active inflammatory process. Scleroderma can be 5 localized or systemic; vascular lesions are common and endothelial cell injury in the microvasculature is an early and important event in the development of systemic sclerosis; the vascular injury may be immune mediated. An immunologic basis is implied by the presence of mononuclear cell infiltrates in the cutaneous lesions and the presence of anti-nuclear antibodies in many patients. ICAM-1 is often 10 upregulated on the cell surface of fibroblasts in skin lesions suggesting that T cell interaction with these cells may have a role in the pathogenesis of the disease. As well as T cells, monocytes/macrophages are proposed to play a role in the progression of scleroderma by secreting fibrogenic cytokines (Yamamoto et al., 2001 J Dermatol Sci 26(2): 133-139). Other organs involved include: the gastrointestinal tract: smooth muscle atrophy and fibrosis resulting in abnormal peristalsis/motility; kidney: concentric 15 subendothelial intimal proliferation affecting small arcuate and interlobular arteries with resultant reduced renal cortical blood flow, results in proteinuria, azotemia and hypertension; skeletal muscle: atrophy, interstitial fibrosis; inflammation; lung: interstitial pneumonitis and interstitial fibrosis; and heart: contraction band necrosis, scarring/fibrosis.

Idiopathic inflammatory myopathies including dermatomyositis, polymyositis and others are 20 disorders of chronic muscle inflammation of unknown etiology resulting in muscle weakness. Muscle injury/inflammation is often symmetric and progressive. Autoantibodies are associated with most forms. These myositis-specific autoantibodies are directed against and inhibit the function of components, proteins and RNA's, involved in protein synthesis.

Sjögren's syndrome is due to immune-mediated inflammation and subsequent functional 25 destruction of the tear glands and salivary glands. The disease can be associated with or accompanied by inflammatory connective tissue diseases. The disease is associated with autoantibody production against Ro and La antigens, both of which are small RNA-protein complexes. Lesions result in keratoconjunctivitis sicca, xerostomia, with other manifestations or associations including biliary cirrhosis, peripheral or sensory neuropathy, and palpable purpura.

Systemic vasculitis are diseases in which the primary lesion is inflammation and subsequent 30 damage to blood vessels which results in ischemia/necrosis/degeneration to tissues supplied by the affected vessels and eventual end-organ dysfunction in some cases. Vasculitis can also occur as a secondary lesion or sequelae to other immune-inflammatory mediated diseases such as rheumatoid arthritis, systemic sclerosis, etc., particularly in diseases also associated with the formation of immune complexes. Diseases in the primary systemic vasculitis group include: systemic necrotizing vasculitis: polyarteritis nodosa, 35 allergic angiitis and granulomatosis, polyangiitis; Wegener's granulomatosis; lymphomatoid granulomatosis; and giant cell arteritis. Miscellaneous vasculitides include: mucocutaneous lymph node syndrome (MLNS or Kawasaki's disease), isolated CNS vasculitis, Behet's disease, thromboangiitis obliterans (Buerger's disease) and cutaneous necrotizing venulitis. The pathogenic mechanism of most of

the types of vasculitis listed is believed to be primarily due to the deposition of immunoglobulin complexes in the vessel wall and subsequent induction of an inflammatory response either via ADCC, complement activation, or both.

5 Sarcoidosis is a condition of unknown etiology which is characterized by the presence of epithelioid granulomas in nearly any tissue in the body; involvement of the lung is most common. The pathogenesis involves the persistence of activated macrophages and lymphoid cells at sites of the disease with subsequent chronic sequelae resultant from the release of locally and systemically active products released by these cell types.

10 Autoimmune hemolytic anemia including autoimmune hemolytic anemia, immune pancytopenia, and paroxysmal nocturnal hemoglobinuria is a result of production of antibodies that react with antigens expressed on the surface of red blood cells (and in some cases other blood cells including platelets as well) and is a reflection of the removal of those antibody coated cells via complement mediated lysis and/or ADCC/Fc-receptor-mediated mechanisms.

15 Thyroiditis including Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, and atrophic thyroiditis, are the result of an autoimmune response against thyroid antigens with production of antibodies that react with proteins present in and often specific for the thyroid gland. Experimental models exist including spontaneous models: rats (BUF and BB rats) and chickens (obese chicken strain); inducible models: immunization of animals with either thyroglobulin, thyroid microsomal antigen (thyroid peroxidase).

20 Inflammatory and Fibrotic Lung Disease, including Eosinophilic Pneumonias; Idiopathic Pulmonary Fibrosis, and Hypersensitivity Pneumonitis may involve a disregulated immune-inflammatory response. Inhibition of that response would be of therapeutic benefit.

Psoriasis is a T lymphocyte-mediated inflammatory disease. Lesions contain infiltrates of T lymphocytes, macrophages and antigen processing cells, and some neutrophils.

25 Other diseases in which intervention of the immune and/or inflammatory response have benefit are infectious disease including but not limited to viral infection (including but not limited to AIDS, hepatitis A, B, C, D, E and herpes) bacterial infection, fungal infections, and protozoal and parasitic infections. Molecules (or derivatives/agonists) which stimulate the immune reaction can be utilized therapeutically to enhance the immune response to infectious agents), diseases of immunodeficiency 30 (molecules/derivatives/agonists) which stimulate the immune reaction can be utilized therapeutically to enhance the immune response for conditions of inherited, acquired, infectious induced (as in HIV infection), or iatrogenic (*i.e.*, as from chemotherapy) immunodeficiency, and neoplasia.

It has been demonstrated that some human cancer patients develop an antibody and/or monocyte/macrophage response to antigens on neoplastic cells. It has also been shown in animal models 35 of neoplasia that enhancement of the immune response can result in rejection or regression of that particular neoplasm. Molecules that enhance the monocyte/macrophage response have utility *in vivo* in enhancing the immune response against neoplasia. Molecules which enhance the monocyte/macrophage proliferative response (or small molecule agonists or antibodies that affected the same receptor in an

agonistic fashion) can be used therapeutically to treat cancer. Molecules that inhibit the monocyte/macrophage response also function *in vivo* during neoplasia to suppress the immune response to a neoplasm; such molecules can either be expressed by the neoplastic cells themselves or their expression can be induced by the neoplasm in other cells. Antagonism of such inhibitory molecules (either with 5 antibody, small molecule antagonists or other means) enhances immune-mediated tumor rejection.

Additionally, inhibition of molecules with proinflammatory properties may have therapeutic benefit in reperfusion injury; stroke; myocardial infarction; atherosclerosis; acute lung injury; hemorrhagic shock; burn; sepsis/septic shock; acute tubular necrosis; endometriosis; degenerative joint disease and pancreatitis.

10 The compounds of the present invention, *e.g.*, polypeptides or antibodies, are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation (intranasal, intrapulmonary) routes. Intravenous or inhaled administration of polypeptides and antibodies 15 is preferred.

20 In immunoadjuvant therapy, other therapeutic regimens, such administration of an anti-cancer agent, may be combined with the administration of the proteins, antibodies or compounds of the instant invention. For example, the patient to be treated with the immunoadjuvant of the invention may also receive an anti-cancer agent (chemotherapeutic agent) or radiation therapy. Preparation and dosing 25 schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in *Chemotherapy Service* Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992). The chemotherapeutic agent may precede, or follow administration of the immunoadjuvant or may be given simultaneously therewith. Additionally, an anti-estrogen compound 25 such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616812) may be given in dosages known for such molecules.

30 It may be desirable to also administer antibodies against other immune disease associated or tumor associated antigens, such as antibodies which bind to CD20, CD11a, CD18, ErbB2, EGFR, ErbB3, ErbB4, or vascular endothelial factor (VEGF). Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be coadministered to the patient. Sometimes, it may be beneficial to also administer one or more cytokines to the patient. In one embodiment, the PRO polypeptides are coadministered with a growth inhibitory agent. For example, the growth inhibitory agent may be administered first, followed by a PRO polypeptide. However, simultaneous administration or administration first is also contemplated. Suitable dosages for the growth 35 inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth inhibitory agent and the PRO polypeptide.

For the treatment or reduction in the severity of immune related disease, the appropriate dosage of an a compound of the invention will depend on the type of disease to be treated, as defined above, the

severity and course of the disease, whether the agent is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments.

5 For example, depending on the type and severity of the disease, about 1 μ g/kg to 15 mg/kg (e.g., 0.1-20 mg/kg) of polypeptide or antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 μ g/kg to 100 mg/kg or more, depending on the factors mentioned above. 10 For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

O. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials (e.g., comprising a PRO molecule) useful for the diagnosis or treatment of the disorders described above is 15 provided. The article of manufacture comprises a container and an instruction. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The 20 active agent in the composition is usually a polypeptide or an antibody of the invention. An instruction or label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, 25 including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

P. Diagnosis and Prognosis of Immune Related Disease

Cell surface proteins, such as proteins which are overexpressed in certain immune related diseases, are excellent targets for drug candidates or disease treatment. The same proteins along with secreted proteins encoded by the genes amplified in immune related disease states find additional use in the 30 diagnosis and prognosis of these diseases. For example, antibodies directed against the protein products of genes amplified in multiple sclerosis, rheumatoid arthritis, or another immune related disease, can be used as diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used to qualitatively or quantitatively detect the expression of proteins encoded by amplified or overexpressed genes ("marker 35 gene products"). The antibody preferably is equipped with a detectable, e.g., fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. These techniques are particularly suitable, if the overexpressed gene encodes a cell surface protein. Such binding assays are performed essentially as described above.

5 *In situ* detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent for those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

10 The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

15 All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

15 Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Microarray analysis of monocyte/macrophages.

20 Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a 25 particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (in this instance, differentiated macrophages) sample is greater than hybridization signal of a probe from a control (in this instance, non-differentiated monocytes) sample, the gene or genes expressed in the test tissue are identified. The implication of this result is that an overexpressed protein in a test tissue is useful not only as a diagnostic marker for the presence of the 30 disease condition, but also as a therapeutic target for treatment of the disease condition.

35 The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

35 In this experiment, CD14+ monocytes are selected by positive selection according to Miltenyi MACS™ protocol. Lymphocytes in 100 ml heparinized blood are separated using Ficoll Paque™. Cells are washed twice in PBS/0.5% BSA/2 mM EDTA. In final wash, all gradients are pooled and volume is brought to approximately 10 ml. The cells are centrifuged, the supernatant is removed and the cell pellet

is resuspended in buffer in a total volume of 10e7 cells per 80 μ l buffer. Add 20 μ l CD14 microbeads per 10e7 total cells, mix and incubate 15 minutes at 6-12 $^{\circ}$ C. Wash the cells by adding 20x labeling volume of buffer, spin pellet and resuspend in 500 μ l buffer per 10e8 cells. Separate cells with MACSTM depletion column type D and check purity of cells by labeling with anti-CD45 and anti-CD14 antibodies (cell purity 5 at this point is >95%). Lyse cells in RNA lysis buffer to obtain a timepoint of Day 0 monocytes, then plate remaining cells in 6 well plates in macrophage differentiation medium: DMEM 4.5 ug/ml glucose, Pen-Strep, L-glutamine, 20% FBS and 10% Human AB serum (Gemini, Cat # 100-512). Seed cells at 1.5 x 10e6 per well (6 well Costar cell culture plates) and grow at 37 $^{\circ}$ C, 7% CO₂. After 24 hours in culture, the cells were harvested and lysed in RNA lysis buffer to obtain mRNA for the Day 1 timepoint. The 10 remaining cells were kept in culture and until Day 7. After 7 days in culture, the cells were lysed in RNA lysis buffer to obtain Day 7 timepoint at which time the cells displayed gross macrophage morphology.

The mRNA was isolated by Qiagen miniprep and analysis run on AffimaxTM (Affymetrix Inc. Santa Clara, CA) microarray chips and proprietary Genentech microarrays. The cells harvested at Day 0 15 timepoint, the Day 1 timepoint, and the Day 7 timepoint were subjected to the same analysis. Genes were compared whose expression was upregulated at Day 7 as compared to Day 0 and Day 1.

Below are the results of these experiments, demonstrating that various PRO polypeptides of the present invention are differentially expressed in differentiated macrophages at Day 7 as compared to non-differentiated monocytes at Day 0 and at Day 1. As described above, these data demonstrate that the PRO 20 polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more immune disorders, but also serve as therapeutic targets for the treatment of those immune disorders. Specifically, the cDNAs shown Figures 592, Figure 708, Figure 724, Figure 888, Figure 1095, Figure 1109, Figure 1456 and Figure 2331 are significantly overexpressed in differentiated macrophages as compared to non-differentiated monocytes at Day 0 and Day 1.

25 The Figures 1-2517 show the nucleic acids of the invention and their encoded PRO polypeptides that are differentially expressed in differentiated macrophages at Day 7 as compared to non-differentiated monocytes at Day 0 and at Day 1.

EXAMPLE 2: Use of PRO as a hybridization probe

30 The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

35 Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42 $^{\circ}$ C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42 $^{\circ}$ C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 3: Expression of PRO in *E. coli*

5 This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable 10 vector is pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and 15 dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

20 Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

25 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain 30 restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq)). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are 35 then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5 .36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately

20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

35 EXAMPLE 4: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-PRO.

5 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μ g pRK5-PRO DNA is mixed with about 1 μ g DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 μ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, 10 dropwise, 500 μ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

15 Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μ Ci/ml ³⁵S-cysteine and 200 μ Ci/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may 20 undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

25 In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 78:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, 30 washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μ g/ml bovine insulin and 0.1 μ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

35 In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 promoter/enhancer containing vector containing a selection marker such as DHFR 5 for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 promoter/enhancer containing vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni^{2+} -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in 10 CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

15 Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and 20 uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

25 Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Qiagen), Dospel[®] or Fugene[®] (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

30 The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mL of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any 35 suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6

mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto

5 columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the

10 column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine

(Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows.

15 The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ l of 1 M Tris buffer, pH 9.

20 The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 5: Expression of PRO in Yeast

25 The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the

30 ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be

35 analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

5

EXAMPLE 6: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus 10 expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with 15 primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfected the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin 20 (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity 25 chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) 30 and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which 35 elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase

(Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

5 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 7: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for 10 instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms.

15 Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti- 20 PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The 25 fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in 30 the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion 35 chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 8: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO

5 polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is 10 covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a 15 fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

20 A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotropic such as urea or thiocyanate ion), and PRO polypeptide is collected.

25

EXAMPLE 9: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell 30 surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested.

35

Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an

agent with an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO 5 polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on 10 September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing 15 antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

20

EXAMPLE 10: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or 25 stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of a PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide 30 must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and 35 Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon

which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically 5 or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

10 The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable 15 the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

What is claimed:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence identity to:

5

- (a) the nucleotide sequence shown in any one of the Figures 1-2517 (SEQ ID NOS: 1-2517); or
- (b) the nucleotide sequence encoding the polypeptide shown in any one of the Figures 1-2517 (SEQ ID NOS: 1-2517).

10

2. A vector comprising the nucleic acid of Claim 1.

3. The vector of Claim 2 operably linked to control sequences recognized by a host cell transformed with the vector.

15

4. A host cell comprising the vector of Claim 2.

5. The host cell of Claim 4, wherein said cell is a CHO cell, an *E.coli* cell or a yeast cell.

20

6. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 5 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

7. An isolated polypeptide having at least 80% amino acid sequence identity to:

25

- (a) a polypeptide shown in any one of Figures 1-2517 (SEQ ID NOS: 1-2517); or
- (b) a polypeptide encoded by the full length coding region of the nucleotide sequence shown in any one of Figures 1-2517 (SEQ ID NOS: 1-2517).

30

8. A chimeric molecule comprising a polypeptide according to Claim 7 fused to a heterologous amino acid sequence.

9. The chimeric molecule of Claim 8, wherein said heterologous amino acid sequence is an epitope tag sequence or an Fc region of an immunoglobulin.

35

10. An antibody which specifically binds to a polypeptide according to Claim 7.

11. The antibody of Claim 10, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

12. A composition of matter comprising (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, in combination with a carrier.

5

13. The composition of matter of Claim 12, wherein said carrier is a pharmaceutically acceptable carrier.

14. The composition of matter of Claim 13 comprising a therapeutically effective amount of
10 (a), (b), (c) or (d).

15. An article of manufacture, comprising:

a container;
a label on said container; and

15 a composition of matter comprising (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide, contained within said container, wherein label on said container indicates that said composition of matter can be used for treating an immune related disease.

20 16. A method of treating an immune related disorder in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of (a) a polypeptide of Claim 7, (b) an agonist of said polypeptide, (c) an antagonist of said polypeptide, or (d) an antibody that binds to said polypeptide.

25 17. The method of Claim 16, wherein the immune related disorder is systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, a spondyloarthropathy, systemic sclerosis, an idiopathic inflammatory myopathy, Sjögren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, thyroiditis, diabetes mellitus, immune-mediated renal disease, a demyelinating disease of the central or peripheral nervous system,
30 idiopathic demyelinating polyneuropathy, Guillain-Barré syndrome, a chronic inflammatory demyelinating polyneuropathy, a hepatobiliary disease, infectious or autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, sclerosing cholangitis, inflammatory bowel disease, gluten-sensitive enteropathy, Whipple's disease, an autoimmune or immune-mediated skin disease, a bullous skin disease, erythema multiforme, contact dermatitis, psoriasis, an allergic disease, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, an immunologic disease of the lung, eosinophilic pneumonias,
35 idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, a transplantation associated disease, graft rejection or graft-versus-host-disease.

18. A method for determining the presence of a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), in a sample suspected of containing said polypeptide, said method comprising exposing said sample to an anti-PRO antibody, where the and determining binding of said antibody to a component of said sample.

5

19. A method of diagnosing an immune related disease in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher 10 or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

20. A method of diagnosing an immune related disease in a mammal, said method comprising (a) contacting a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), anti-PRO antibody with a test sample of tissue cells obtained from said mammal and (b) detecting the formation of a complex between the antibody and the polypeptide in the test sample, wherein formation of said complex is indicative of the presence of an immune related disease in the mammal from which the test tissue cells were obtained.

20

21. A method of identifying a compound that inhibits the activity of a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally respond to said polypeptide with (a) said polypeptide and (b) a candidate compound, 25 and determining the lack responsiveness by said cell to (a).

22. A method of identifying a compound that inhibits the expression of a gene encoding a PRO polypeptide of the invention as described in Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally express said polypeptide with a candidate compound, and 30 determining the lack of expression said gene.

23. The method of Claim 22, wherein said candidate compound is an antisense nucleic acid.

24. A method of identifying a compound that mimics the activity of a PRO polypeptide of 35 the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), said method comprising contacting cells which normally respond to said polypeptide with a candidate compound, and determining the responsiveness by said cell to said candidate compound.

25. A method of stimulating the immune response in a mammal, said method comprising administering to said mammal an effective amount of a PRO polypeptide of the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), antagonist, wherein said immune response is stimulated.

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26. A method of diagnosing an inflammatory immune response in a mammal, said method comprising detecting the level of expression of a gene encoding a PRO polypeptide of the invention as described in any one of Figures 1-2517 (SEQ ID NOS: 1-2517), (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, 10 wherein a higher or lower level of expression of said gene in the test sample as compared to the control sample is indicative of the presence of an inflammatory immune response in the mammal from which the test tissue cells were obtained.

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27. A method of differentiating monocytes comprising;

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- (a) isolating a population of monocytes;
- (b) contacting the monocytes with an effective amount of a PRO polypeptide of the invention as described in any of Figures 1-2517 (SEQ ID NOS: 1-2517); and
- (c) determining the differentiation of said monocytes to said PRO polypeptide.

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FIGURE 1

CATCCGGTGTGGTCGACGGGCTCCAAGAGTTGGGCGCGGACCGGAGTACCTGCGTGCAGTT**ATGTCGGCG**
TCGGTAGTGTCTGTCATTCGGTTCTAGAAGAGTACTTGAGCTCCACTCCGAGCGTCTGAAGTTGCTGGAC
GCGTACCTGCTGTATATACTGCTGACGGGGCGCTGCAGTCGGTTACTGTCCTCGTGGGACCTTCCCCTTC
AACTCTTCTCTCGGGCTTCATCTCTTGTGTGGGAGTTCATCCTAGCGGTTGCCTGAGAATACAGATCAAC
CCACAGAACAAAGCGGATTCCAAGGCATCTCCCAGAGCGAGCCTTGCTGATTTCATTTGCCAGCACCATC
CTGCACCTGTTGTCACTGAACCTTGGC**TGA**TCATTCTCATTTACTTAATTGAGGAGTAGGAGACTAAAAGA
ATGTTCACTCTTGAATTCTGGATAAGAGTTCTGGAGATGGCAGCTTATTGGACACATGGATTTCTTCAGAT
TTGACACTTACTGCTAGCTGCTTTATGACAGGGAGAAAAGCCCAGAGTTCACTGTGTGTCAGAACAACTTTC
TAACAAACATTATTAAATCCAGCCTGCCTTCATTAAATGTAACCTTGCTTCAAATTAAAGAACTCCAT
GCCACTCCTCAAAAAAAAAAAAAAA

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FIGURE 2

MSASVVSVISRFLEEYLSSTPQRLKLLDAYLLYILLTGALQFGYCLLVGTFPFNSFLSGFISCVGSFILAVCLRI
QINPQNKAQFQGISPERAFADFLFASTILHLVVVMNFVG

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FIGURE 3

CTCCGGCGCAGTGTGGGACTGTCTGGGTATCGGAAAGCAAGCCTACGTTGCTCACTATTACGTATAATCCTTT
CTTTCAAGATGCTGAGGATGCACCATGGAGGAGGATTTGCTTCAGGAATTG
CAACTCATGTCCCTCATCATCAATACCTCTATTCAACAAGGAGATTTCCTCGGGAGTTGATCTCTAATGCT
TCTGATGCCCTGGACAAGATTGCTATGAGAGCCTGACAGACCCCTCGAAGTTGGACAGTGGTAAAGAGCTGAAA
ATTGACATCATCCCCAACCTCAGGAACGTACCCCTGACTTTGGTAGACACAGGCATTGGCATGACCAAGCTGAT
CTCATAAATAATTGGGAACCATTGCCAAGTCTGGTACTAAAGCATTGAGGGCTTCAGGCTGGCAGAC
ATCTCCATGATTGGGAGTTGGTGTGGCTTTATTCTGCCTACTTGGTGGCAGAGAAAGGGTTGTGATCACA
AAGCACAAACGATGATGAACAGTATGCTGGAGTCTCTGCTGGAGGTTCTCACTGTGCGTGTGACCATGGT
GAGCCATTGGCAGGGGTACCAAAGTGATCCTCCATCTAAAGAAGATCAGACAGAGTACCTAGAAGAGAGCGG
GTCAAAGAAGTAGTGAAGAACGATTCTCAGTTGCTAGGCTATCCCATACCCTTATTGGAGAAGGAACGAGAG
AAGGAAATTAGTGTGATGAGGCAGAGGAAGAGAAAGGTGAGAAAGAGAGAAGATAAAGATGATGAAGAAAAA
CCCAAGATCGAAGATGTGGGTCAGATGAGGAGGATGACAGCGTAAGGATAAGAAGAAGAAAACTAAGAAGATC
AAAGAGAAAATACATTGATCAGGAAGAACTAAACAAGACCAAGCCTATTGGACAGAAACCTGATGACATCACC
CAAGAGGAGTATGGAGAATTCTACAAGAGCCTCACTAATGACTGGGAAGACCACTGGCAGTCAGCACTTTCT
GTAGAAGGTCAAGTGGATTAGGGCATTGCATTTATTCTCGTGGCTCCCTTGACCTTTGAGAACAAAG
AAGAAAAGAACACATCAAACACTATGTCGCCGTGTTCATGGACAGCTGTGATGAGTTGATACCAGAG
TATCTCAATTATCCGTGGTGTGGTGACTIONTGGAGGATCTGCCCTGAACATCTCCGAGAAATGCTCCAGCAG
AGCAAAATCTGAAAGTCATTGCAAAACATTGTTAAGAAGTGCCTTGAGCTCTCTGAGCTGGCAGAACAG
AAGGAGAATTACAAGAAATTCTATGAGGCATTCTCTAAACACTCAAGCTTGAATCCACGAAGACTCCACTAAC
CGCCGCCGCCTGTCAGTGCCTGCGCTATCATAACCTCCAGTCTGGAGATGAGATGACATCTCTGTCAGAGTAT
GTTTCTCGCATGAAGGAGACACAGAAGTCCATCTATTACATCACTGGTGAGAGCAAAGAGCAGGTGGCCAAC
GCTTTGTGGAGCGAGTGCAGAACGGGCTCGAGGTGGTATATATGACCGAGCCCATTGACGAGTACTGTG
CAGCAGCTCAAGGAATTGATGGGAAGAGCCTGGTCTCAGTTACCAAGGAGGGCTGGAGCTGCCCTGAGGATGAG
GAGGAGAAGAAGAAGATGGAAGAGAGCAAGGCAAAGTTGAGAACCTCTGCAAGCTCATGAAAGAAATCTTAGAT
AAGAAGGTTGAGAAGGTGACAATCTCAATAGACTTGTGCTTCACCTGCTGCATTGTGACCAGCACCTACGGC
TGGACAGCCAATATGGAGCGGATCATGAAAGCCCAGGCACCTGGGACAACCTCACCATTGGCTATATGATGGCC
AAAAAGCACCTGGAGATCAACCTGACCACCCATTGTGGAGACGCTGCCAGAAGGCTGAGGCCACAAGAAT
GATAAGGCAGTTAAGGACCTGGTGTGCTGTTGAAACCGCCCTGCTATCTCTGGCTTCCCTGAGGAT
CCCCAGACCCACTCCAACCGCATCTATCGCATGATCAAGCTAGGTCTAGGTATTGATGAAGATGAAGTGGCAGCA
GAGGAACCCAATGCTGCAGTCCCTGATGAGATCCCCCTCTCGAGGGCGATGAGGATGCGCTCGCATGGAAGAA
GTCGATTAGGTTAGGATTGCTGCAGC
TCGAGTGCCCCCTGCCCCACCTGGCTCCCCCTGCTGGTGTCTAGTGTGTTTCCCTCTGTCCTTGTGAA
GGCAGTAAACTAAGGGTGTCAAGCCCCATTCCCTCTACTCTTGACAGCAGGATTGGATTTGTGATTGTGAA
TTATTTATTTCTCATTTGTTCTGAAATTAAAGTATGCAAATAAGAATATGCCGTTAAAAAAAAAAAAAA

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FIGURE 4

MPEEVHHGEEEVETFAFQAEIAQLMSLIINTFYSNKEIFLRELISNASDALDKIRYESLTDPSKLDGKELKIDI
IPNPQERTLTLVDTGIGMTKADLINNLGTIAKSGTKAFMEALQAGADISMIGQFGVGFYSAYLVAEKVVVITKHN
DDEQYAWESSAGGSFTVRADHGEPIGRGTVKVLHLKEDQTEYLEERRVKEVVKHSQFIGYPITLYLEKEREKEI
SDDEAEEEKGEKEEEDKDDEEKPKIEDVGSDEEDDSGKDKKKTKKIKEKYIDQEELNKTAPIWTRNPDDITQEE
YGEFYKSLTNDWEDHLAVKHF SVEGQLEFRALLFIPRRAPFDLFENKKKNNIKLYVRRVFIMDSCDELIPEYLN
FIRGVVDSEDLPLNISREMLQQSKILKVKIRKNIVKKCLELFSLAEDKENYKKFYEAFSKNLKLGIHEDSTNRRR
LSELLRYHTSQSGDEMTSLSEYVSRMKETQKSIYYITGESKEQVANSAFVERVRKRGFEVVYMTEPIDEYCVQQL
KEFDGKSLVSVTKEGLELPEDEEEKKMEESEKAKFENLCKLMKEILDKKVEKVTISNRLVSSPCCIVTSTYGWTA
NMERIMKAQALRDNSTMGYMMAKKHLEINPDHPIVETLRQKAEDKNDKAVKDLVVLLFETALLSSGFSLDPQT
HSNRIYRMIKLGIDEDEVAEEPNAAVPDEIPPLEGDEDASRMEEVD

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FIGURE 5

ATGCAGGCCACGGAGCTCGCGTGGCATCGACCTGGCACCACTACTCGCGTGGCGTTTTCAGCAGGGCCGCTGGAGATCCTGGCCAACGACCAGGGCAACCGCACACGCCAGCTACGTGGCTTCACCGACACCGAGCGCTGGTGGGGACGCGGCCAAGAGCAGGCGGGCCTGAACCCCCACAACACCGTGTTCGATGCCAAGCGGCTGATCGGGCGCAAGTTCGCGACACCACGGTGCAGTCGGACATGAAGCAGTGGCCCTCCGGTGGTGAGCAGGGCGCAAGCCCAAGGTGCGGTATCGTCCATGGTGTGAGCAAGATGAAGGAGACGGCGAGGCAGCTGGCCAGCCCAGTGGCTACCTGGCCAGCCCAGTGGCTGAAGCACGCAGTGTACCGTGCCTGGGAGAGCGCAACGTGTTGCGGATCATCATGAGGCCACGGCAGCTGCCATGCCATGGCTGGGACCCGGGAGAGCGCAACGTGCTATTTTGGACCTGGGTGGGGCACCTCGATGTGCGTTCTCCATTGACGCTGGTGTCTTGAGGTGAAAGCCACTGCTGGAGATAACCACCTGGGAGGAGGACTTCGACAACCGGCTCGTAACCACCTCATGGAAGAATTCCGGCGGAAGCATGGGAAGGACCTGAGCGGAACAAGCGTGCCTCGGCAGGCTGCGCACAGCCTGTGAGCGGCCAAGCGCACCCTGCTCCAGCACCCAGGCCACCTGGAGATAGACTCCCTGTCAGGGCGTGGACTTCTACACGTCCATCACTCGTCCCCGTTGAGGAACTGTGCTCAGACCTCTCCGCAGCACCCCTGGAGGCCGGTGGAGAAGGCCCTGCGGATGCCAGCTGGACAAGGCCAGATTCATGACGTCGTCCTGGTGGGGGCTCACTCGCATCCCCAAGGTGCGAGAAGTTGCTGAGGACTTCTCAACGGCAAGGAGCTGAACAAGAGCATCAACCTGTGAGGCTGTGGCTATGGGGCTGGTGCAGGACTTCTGGGCTGGAGACAGCAGGTGGGGTGTGACGACAGGCTGATCCAGAGGAACGCCACTATCCCCACCAAGCAGACCCAGACTTCAACCACCTACTCGGACAACCAGCCTGGGTCTTCATCCAGGTGTATGAGGGTGAGAGGGCCTATGAGGACAACCAACCTGCTGGGGCTTGTGAACTCAGTGGCATCCCTCTGCCAACGTGGAGTCCCCCAGATAGAGGTGACCTTGACATTGATGCTAATGGCATCCTGAGCGTGACAGCCACTGACAGGAGCACAGGTAAAGGTAAGGTAACAAAGATCACCATACCAATGACAAGGGCCGGCTGAGCAAGGAGGAGGTGGAGAGGATGGTCATGAAGCCGAGCAGTACAAGGCTGAGGATGAGGCCAGAGGACAGAGTGGCTGCCAAAAACTCGCTGGAGGCCATGTCTTCCATGTGAAAGGTTCTTGCAAGAGGAAGCCTTAGGGACAAGATCCCGAAGAGGACAGGCGCAAAATGCAAGACAAGTGTCGGGAAGTCCTGGCTGGAGCACAACCAGCTGGCAGAGAAGGAGGAGTATGAGCATCAGAAGAGGGAGCTGGAGCAAATCTGTCGCCCCATCTCTCCAGGCTCTATGGGGGGCTGGTGTCCCTGGGGCAGCAGTTGTGGACTCAAGCCGCCAGGGGACCCCAGCACCGCCCCATCATTGAGGAGGTTGATTGA

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FIGURE 6

MQAPRELAVGIDLGTTYSCGVFQQGRVEILANDQGNRTTPSYVAFTDTERLVGDAAKSQAALNPHTNVFDAKRL
IGRKFADTTVQSDMKHWPFRVVSEGGKPKVPVSYRGEDKTFYPEEISSMVLSKMKETAEAYLGQPVKHAVITVPA
YFNDSQRQATKDAGAIAGLNVLRIINEPTAAAIAYGLDRRGAGERNVLIFDLGGGTFDVSVLSIDAGVFEVKATA
GDTHLGGEDFDNRLVNHFMEEFRRKHGKDLSGNKRALGRLRTACERAKRTLSSSTQATLEIDSFEGVDFYTSIT
RARFEELCSDLFRSTLEPVEKALRDAKLDKAQIHDDVVLVGGSTRIPKVQKLLQDFNGKELNKSINPDEAVAYGA
AVQAAVLMGDKCEKVQDLLLLDVAPLSLGLETAGGVMTTLIQRNATIPTKQTQTFTTYSDNQPGVFIQVYEGERA
MTKDNNLLGRFELSGIPPAPRGVPQIEVTFDIDANGILSVTATDRSTGKANKITITNDKGRLSKEEVERMVHEAE
QYKAEDEAQRDRVAAKNSLEAHVFHVKGSLQEESLRDKIPEEDRRKMQDKCREVILAEHNQLAEEKEYEHQKRE
LEQICRPIFSRLYGGPGVPGGSSCGTQARQGDPSTGPIIEEV

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FIGURE 7A

TGCGACCGCCTCCCTGCGCCCGCCCCCTCCGGCTAGCTCGCTGGCTCCGGCTCTCCGACGTCTCCTACCTCC
 TCACGGCTCTTCCCGCGCTCCTGGCTCCCTCTGCCCGAGCTCCGTCTGGCGGGCAGGGCAGTGCAGTG
 GTGCAGA**ATGG**GCTGACCTCAGTCTGAGATGCATTAACAGAACCATCTCCAGACATTGAGGGAGAGATAAGCG
 GGACTTCATTGCCACACTAGAGGCAGAGGCCTTGATGATGTTGAGGAAACTGTTGAAAACAGACTATAT
 TCCTCTCTGGATGTTGATGAGAAAACCGGAACTCAGAGTCAAAGAGAACAGGAAACTGCTCAGAAACTAGCCAGAT
 TGAAGATACTCCATCTTCAAACACTCCTAGCCAATGGTGGTCATGGAGTAGAAGGGAGCGATACTACAGG
 GTCTCCAACCTGAATTCCCTGAAGAGAAAATGGCTACCAGGAATACCCAAATAGCCAGAACTGGCCAGAAGATAAC
 CAACTTTGTTCAACCTGAGCAAGTGGTCATCCTATCCAGACTGATCCCTTAAGATGTACCATGATGATGA
 CCTGGCAGATTGGCTTCCCTCAGTGCACAGCTGATACTCAATATTCAGGACAAAATGATCCCTGAA
 AGACAGTTACGGTATGTCCTCTGCAACACAGCTGTTGACCTCAGGGTGGCTGTGGAAGCCTAAACTCTCC
 ACACTCAGAGTCCTTGTTCAGGGCTGAGCAACCTCCTCAGCCAACGGCAGTCCCTAGAGCTAGC
 CAAGGAGATAGAAAATGGCATCAGAAGAGAGGCCACCAGCACAAAGCATTGAAATAATGATGGACTGAAGACTAC
 TGACATGGCACCATCTAAAGAAACAGAGATGGCCCTGCCAAGGACATGGCACTAGCTACAAAACCGAGGTGGC
 ATTGGCTAAAGATATGGAATCACCCACCAAATTAGATGTGACACTGGCAAGGACATGCAGCCATCCATGGAATC
 AGATATGCCCTAGTCAAGGACATGGAACTACCCACAGAAAAAGAAGTGGCCCTGGTTAGGGATGTCAGATGGC
 CACAGAAACAGATGTATCTCAGCCAAGAATGTGGTACTGCCACAGAAACAGAGGTAGCCCAGCCAAGGATGT
 GACACTGTTGAAAGAAACAGAGAGGGCATCTCTATAAAATGGACTTAGCCCCTCCAAGGACATGGACCACC
 CAAAGAAAACAAGAAAGAACAGAGAGGGCATCTCTATAAAATGGACTTGGCTCCTCCAAGGACATGGACC
 ACCCAAAGAAAACAAGATAGTCCCAGCCAAGGATTGGTATTACTCTCAGAAATAGAGGTGGCACAGGCTAATGA
 CATTATATCATCCACAGAAATATCCTCTGCTGAGAAGGTGGCTTGTCTCAGAAACAGAGGTAGCCCTGGCCAG
 GGACATGACACTGCCCGGAAACCAACGTGATCTTGACCAAGGATAAGCACTACCTTAAAGCAGAGGTGGC
 CCCAGTCAGGACATGGCTCAACTCCCAGAAACAGAAATAGCCCCGCAAGGATGTGGCTCGTCCAGTAAA
 AGAAGTGGCTTGTGAAGGACATGTCTCCACTATCAGAAACAGAAATGGCTCTGGCAAGGATGTGACTCCACC
 TCCAGAACAGAAGTAGTTCTCATCAAGAACGTATGTCCTCCAGAAATGGAGGTGGCCCTGACTGAGGATCA
 GGTCCCAGCCCTCAAAACAGAACGACCCCTGGCTAAGGATGGGTTCTGACCCCTGGCAACAATGTGACTCCAGC
 CAAAGATGTTCCACCACTCTCAGAAACAGAGGCAACACCAGTCCAATTAAAGACATGGAAATTGACAAAACACA
 AAAAGGAATAAGTGAGGATTCCATTAGAATCTGCAAGGATGTGGGCAGTCAGCTGCACCTACTTCTATGAT
 TTCACCAGAAACCATCACAGGAACGGGAAAAGTGCAGCTGCGCCGAGGAGGATTCTGTTAGAAAAACT
 AGGGGAAAGGAAACCATGCAACAGTCAACCTCTGAGCTTCTCAGAGACCTCAGGAATAGCCAGGCCAGAAGA
 AGGAAGGCCTGTGGTAGTGGGACAGGAAATGACATCACCACCCCAACGAAAGGAGCTCCACCAAGCCCAGA
 GAAGAAAACAAAGCCTTGGCCACCCTCAACCTGCAAAGACTCAACATGAAAGCAGACAGCCACTTC
 TCTCCCTAAGCAGCCAGCTCCCACCACATTGGGGTTGAATAAAAACCCATGAGCCTGCTCAGGCTTAGT
 GCCAGCTGCCCAACCCAAACGCCCTGCGCTGCCCTGCCAGGGCTTCCATCTTACCTCAAAAGACGTGAAGGCC
 AAAGCCCATTGCAGATGCAAAGGCTCTGAGAAGCGGGCTCACCATCCAAGCCAGCTCTGCCCCAGCCTCCAG
 ATCTGGGTCCAAGAGCACTCAGACTGTTGCAAAAACACAAACAGCTGCTGCTGCTCAACTGGCCAAGCAG
 TAGGAGCCCTCCAGCTCTGCCAAGAAGCCCAGTCCATTAAAGACTGAGGGAAACCTGAGAAGTCAAGAA
 GATGACTGCAAAGTCTGTACAGCTGACTTGAGTCGCCAAAGAGCACCTCCACCGAGTCCATGAAGAAAACAC
 CACTCTCAGTGGGACAGCCCCGCTGCAGGGTGGTCCCAGCCAGTCAAGGCCACACCCATGCCCTCCGGCC
 CTCCACAACTCTTCTAGACAAGAACCCACCTCGCCAACCCAGCTCCACCAACCCCCGGCTCAGCCGCC
 GCCACCAATACTCTGCTCTGATCTGAAGAATGTCGCTCCAAGGTTGGCTCCACGGAAAACATCAAGCATCA
 GCCTGGAGGAGGCCGGCAAAGTAGAGAAAAACAGAGGAGCTGCTACAACCGAAAGCCTGAATCTAATGC
 AGTCACTAAAACAGCCGGCCAATTGCAAGTGCACAGAAACACCTGCGGGAAAGTCCAGATAGTCTC
 AGTGAAGCTACAGCCATATTCAAGTGTGGTCCAAGGACAATATTAAGCATGTCCCTGGAGGTGTAATGT
 TCAGATTCAAGAACAGAAAAGTGGACATCTCAAGGTCTCCCAAGTGTGGTCTAAGGCTAACATCAAGCACAA
 GCCTGGTGGAGGAGATGTCAGAAGATTGAAAGTCAGAACGTTGAAACTCAAGGAGAACGGCCAGGCCAGGTGGGATC
 CCTCGATAATGTGGGCCACCTACCTGCAGGAGGTGCTGTGAAGACTGAGGGCGGTGGCAGCGAGGCTCTGTG
 TCCGGGTCCCCCTGCTGGGGAGGAGCCGGCATCTGAGGGCAGCGCCTGAAGCTGGGCCCACTTCAGCCAG
 TGGCCTCAATGGCCACCCACCCCTGTCAGGGGGTGGTGAACCAAAGGGAGGCCAGACCTGGACAGCCAGATCCA

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FIGURE 7B

GGAGACAAGCATC**TAAT**GATGACATTCTGGTCTCGTCTCCGTCTCCCCGTGTTCCCTCTGTCTCCCTGTT
CCCCCTCTCCCTTCCCTCCCATGTCAGTGCAGATTGAGACCTACAGGCTGACGTTCCGGCAAATGCCAGGGC
CCGCACCGACCACGGGGCGACATTGTCCTCCGCCCCACACTTCCCTGGCGGCCAACTCGGGCTCCGGGT
CCTTGGCCCCCTTCCGGCTGTCACAGACAGTGAGCGCTGGCGCCGTGGCAGCCGCTAGGCTC
GCCTTCCCTCCTGCTTGCCTGGCCGGCAGCAGCAGCCCTGCCACACCTCCTCACTCCCCAGCCTGGGC
CCATCTCCCTGCTTGGTCTTGCCTCACTGCCTCACTGCTCCGTGGAGGAGGTTGGGAGGGGTTGGGTGG
TTGAGGCTAAGTTGGGATCTAGGAGAGGAACCAGATTCTATCCTCATCTTTGGTTCTTGGTCAAAC
CAAAAGAAAATGACATGCCCTCCCTCCTGGATCTACCTGGAGGGAAAGAGTGGAGGTGGATTCCGAGTGGT
ACAGGACGCTGACCGTGGAGCTTAAGCCACTGCCCTCCCTGGTCCCACAAATGGCGCCCCCCTCCCCAT
GCAGGTGGTGTGGCCCTTGTGCCCTGCCCAAGTTGGGGTCAGTGTGCTGCTGCTGGTCAAACAT
ACCCGCCTAGCTGCTGTACATTTCTGTTGTCCTTTATTTCTAATAACCTAAAATGGCAAAT
AGTTCTGCAGGTTGAAGCCATGTCTACATGAAAGTCCCTCAGTAAGTGTAGAGGGAACAGGGCGGAGATATCCTT
ATGCCACCCCCGCTGGAGGATGTGGGAGCTTAGGGCCCTGGAGGCAGTCGGCAGGGAAAGAGGGGTGCAGAGGC
TGTGGCTGGTGAGCCGGTCAGGCACACAAGGGGCCCTGGAGCAGTGGACTGGTTGGTTGGCATTGGTGT
GTATGCTGCTTTCTTCTAACCAGAGGCTGGTTGGCATCTCTGCTCCATTCCCTGGATCTGGTGGTCAG
CCCTAGGATAAAAGCCAGGGCTGGAGAACAGAAAGGGCCAGGAGATGAATT

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FIGURE 8

MADLSLADALTEPSDIEGEIKRDFIATLEAEAFDDVVGETVGKTDYIPLLDVDEKTGNSESKKPCSETSQIED
TPSSKPTLLANGGGHGVGSDDTGSPTEFLEEKMAYQEYPNQNWPEDTNFCFQPEQVVDPIQTDPFKMYHDDDLA
DLVFPSSATADTSIFAGQNDPLKDSYGMSPCNTAVVPQGWSEALNSPHSESFSPEAVAEPQPTAVPLEAKE
IEMASEERPPAQALEIMMGLKTTDMAPSKETEMALAKDMALATKTEVALAKDMESPTKLDVTLAKDMQPSMESDM
ALVKDMELPTEKEVALVKDVRWPTEDVSSAKNVVLPTETEVAPAKDVTLLKETERASPIKMDLAPS KDMGPPKE
NKKETERASPIKMDLAPS KDMGPPKENKIVPAKDLVLLSEIEVAQANDIISSTEISSAEKVALSSETEVALARDM
TLPPETNVILTKDKALPLEAEVAPVKDMAQLPETEIAPAKDVPSTVKEVGLLKDMSPONSETEALGKDVTPPP
TEVVLIKNVCLPPEMEVALTEDQVPALKTEAPLAKGVLTLANNVTPAKDVPPLSETEATPVIKDMEIAQTQKG
ISEDSHLESLQDVGQSAAPTFMISPETITGTGKKCSLPAEEDSVLEKLGERKPCNSQPSELSETSGIARPEEGR
PVVSGTGNDITTPPNKELPPSPEKKTKPLATTQPAKTSTS KAKTQPTSLPKQPAPTTIGGLNKKPM SLASGLVPA
APPKRPAVASARPSILPSKDVKPPIADAKAPEKRASPSKPASAPASRSGSKSTQTVAKTTAAVASTGPSSRS
PSTLLPKPTAIKTEGKPAEVKKMTAKSVPADLSRPKSTSTSSMKTTLSGTAP AAGVVP SRVKATPMPSPRST
TPFIDKKPTSAKPSSTTPRLSRLATNTSAPDLKNVRSKVGSTENIKHQPGGGRAKVEKKTEAAATTRKPE SNAVT
KTAGPIASAKQPGAGKVQIVSKKVSYS HIQSKCGSKDNIKHVPGGGNVQIQNKKVDISKVSSKCGSKANIKHKG
GGDVKIESQKLNFK EKAQAKVGSLDNVGLPAGGAVKTEGGGSEAPLCPGPPAGEEPAISEAAPEAGAPTSASGL
NGHPTLSGGGDQREAQTLD SQI QETSI

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FIGURE 9

CCGGCACGAGAGGGAGTTGTGAGTTCCAAGCCCCAGCTCACTCTGACCACTTCTGCCTGCCAGCATTGAA
GGGCCTTGCAGCTGCCCTCCTGTCTCGTCTGCACCATGGCCCTCTGCTCTGTGCACAAGTTGGTACCAACAA
AGAGCTCTGCTGCCCTCGTCTATACTCTGGCAGATTCCACAAAAGTTCATAGTTGACTATTCTGAAACCAGCCC
CCAGTGCCCCAAGCCAGGTGTCACTCTCTAACCAAGAGAGGCCGGCAGATCTGTGCTGACCCCAATAAGAAGTG
GGTCCAGAAATACATCAGCGACCTGAAGCTGAATGCC **TGAGGGGCCTG**GAAGCTGCCAGGGGCCAGTGAACCTGG
TGGGCCAGGAGGGAACAGGAGCCTGAGCCAGGGCAATGCCCTGCCACCCCTGGAGGCCACCTCTAAGAGTC
CCATCTGCTATGCCAGCCACATTAACCTAACTTAACTCTGACATCATTTGAAATTGATT
CTATTGTTGAGCTGCATTATGAAATTAGTATTTCTCTGACATCTCATGACATTGCTTATCATCCTTCCCT
TTCCCTTCAACTCTCGTACATTCAATGCATGGATCAATCAGTGTGATTAGCTTCTCAGCAGACATTGTGCCAT
ATGTATCAAATGACAAATCTTATTGAATGGTTGCTCAGCACCACCTTAATATATTGGCAGTACTTATTAT
ATAAAAGGTAAACCAGCATTCTCACTGTGAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 10

MKGGLAAALLVLVCTMALCSCAQVGTNKELCCLVYTSWQIPQKFIVDYSETSPQCPKPGVILLTKRGRQICADPNK
KWVQKYISDLKLNA

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FIGURE 11

ATTCCCGCTCTGCTTCCGGCAGGTGATGGCCTCCCCCGCGGCCTAGAGGTCCAGCGCCGCCGAGCAGCGGA
CAGTCCTCCTGTTGTCGACCGAGAGTCCTGGTGAATTGAACATGCTGGTCCGCTAGCCAAGCTGTCTGC
CTGGCATATCAGTGCTTCATGCCTAAAAATTAAAGAAAATTATCTACCTCTATGTCTATAAGATGGTCTCA
ACTTCTACTGTGCTCGAATTAACCTACCCATTATACTATTATCCCCGGGATAAGGACAAGAGATGGAAAGGAGT
AACATGGAAAGGTTTGCAGAAGAAGCAGATGTTGAATAGTTGGTCAGGCCCTGCAGGGCTCTGCAGCTGTT
CGTCTAAAACAGTGGCTGGCACATGAAAAGGACATCCGTGTGTCTAGTGGAGAAAGCTGCCAGATAGGA
GCTCATACTCTCTCAGGGGCTTGCCTGATCCAGGTGCTTAAAGAACTCTCCCAGACTGGAAAGAGAACGGG
GCTCCACTTAACACTCCTGTAACAGAAGACAGATTGAAATTAAACAGAGAAATACAGAATTCTGTGCCAATT
CTTCCAGGGCTTCCAATGAATAATCATGGCAATTACATTGTACGCTTGGACATTAGTGAGCTGGATGGCGAA
CAAGCAGAAGCCCTGGTGTGAAGTATAACCTGGTTATGCAGCTGCTGAGGTCTTTTATGATGATGGTAGT
GTAAAAGGAATTGCCACTAACGATGTAGGGATACAAAAGGATGGTCACCAAAGGCAACATTGAGAGAGGACTG
GAACATACATGCTAAAGTCACAATTGGCAGAAGGTTGCCATGGACATCTAGCCAAGCAACTATATAAGAAGTT
GATTTGAGAGCAAATTGTGAACTCAAACCTACGGGATTGGACTGAAGGAGTTATGGTTATTGATGAAAAGAAC
TGGAAACCTGGGAGAGTAGATCACACTGTTGGTGGCCTGGACAGACATACCTATGGAGGATCTTCCCTAT
CATTGAAATGAAGGTGAACCCCTAGTAGCTCTGGTCTTGTGGTAGACTATCAGAATCCATACCTGAGT
CCATTTAGAGAGTCCAAAGGTGGAAACACCACCTAGCATTGGCAACCTTGGAAAGGTGGAAAAGGATTGCA
TACGGAGCCAGAGCTCTCAATGAAGGTGGCTTCAGTCTATACCAAAACTCACCTTCTGGTGGTTACTAATT
GGTTGAGTCCTGGTTTATGAATGTTCCAAGATCAAAGGTACTCACACAGCAATGAAAAGTGGAAATTAGCA
GCAGAACTATTAACTCAACTAACTAGTGAAATCTCCAATCAAAGACAATAGGACTCCATGTAACGAAAT
GAGGACAATTGAAGAACTCATGGGTATGGAAAGAGCTATATTCTGTTAGAAATATAAGACCGTCCTGCCACGGA
GTACTGGGTGTATGGAGGGATGATTACACTGGAAATCTTACTGGATATTGAGAGGAATGGAGCCGTGGACT
CTGAAACATAAAGGTCTGACTTGAACGGCTCAAGCCAGCAAGGATTGCACACCTATTGAGTATCCAAAACCC
GATGGACAGATCAGTTGACCTTGTCTGTGACATCTGGCTCTGAGTGGTACTAATCATGAACATGACCAGCCGGCA
CACTTAACCTTAAGGGATGACAGTATACTGTTAAATAGAAATCTGTCGATATATGATGGGCCGAGCAGCGATT
TGTCTGCAGGAGTTATGAATTGTAACCTGTGGAACAAGGTGATGGATTCTGGTTACAGATAATGCTCAGAAC
TGTGTACATTGAAACATGTGATATTAAAGATCCAAGTCAGAATATTAACTGGGTGGTACCTGAAGGTGGAGGA
GGACCTGCTTACAATGGAATGTAACTGCAGCTAGCCAGTTCTTCAAGTATGGCAAGCTAACGTTAAATGTT
TAGAGATTAACAGAATTCTAGAATGTCTTCTGCATATTACTGAACAGAATAGTCACAAAATGATTATCAAATAA
AATTATGTTACTATAAAAAAAAAA

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FIGURE 12

MLVPLAKLSCLAYQCFHALKIKKNYLPLCAIRWSSTSTVPRITTHYTIYPRDKDKRWEVNMERFAEEADVIVG
AGPAGLSAAVRLKQLAVAHEKDIRVCLVEKAAQIGAHTLSGACLDPGAFKELFPDWKEKGAPLNTPVTEDRFGIL
TEKYRIPVPILPGLPMNNHGNYIVRLGHLVSMGEQAEALGVEVPGYAAAEVLFHDDGSVKGIATNDVGIQKDG
APKATFERGLELHAKVTIFAEGCHGLAKQLYKKFDLRANCEPQTYGIGLKELWVIDEKNWKGPRVDHTVGWPLD
RHTYGGSGFLYHLNEGEPLVALGLVVG LDYQNPYLSPEFQRWKHHPSIRPTLEGGKRIAYGARALNEGGFQSIP
KLTFPGGLLIGCSPGFNMVPKIKGTHTAMKSGILAAESIFNQLTSENLQSKTIGLHVTEYEDNLKNSWWKELYS
VRNIRPSCHGVLGVYGGMIYTGIFYWILRGMEPWTLKHKGSDFERLKPDKDCTPIEYPKPDGQISFDLSSVALS
GTNHEHDQPAHLLRDDSIPVNRNLSIYDGPEQRFCPAGVYEFVPVEQGDGFRLQINAQNCVHCKTCDIKDPSQ
INWVVPEGGGGPAYNGM

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FIGURE 13

CTCAGCTCTTGCCTAACCAACTGGAAGGCATTAAAGGACCTCTGCCGCTCAGACCTGCAGTTAACCTCC
 GCCCTGACCCACCCCTCCCGATGCAGTCCCTGATGCAGGCTCCCTCTGATGCCCTGGCTGCTTCGCGA
 CCCCTGCGCAAGCCCACCTGAAAAGCCATCCCAGCTCAGTAGCTTTCTGGATAACTGTGATGAAGGGAAGG
 ACCCTGCGGTGATCAGAACGCTGACTCTGGAGCCTGACCCATCGCTGTTCTGGAAATGTGACCCCTCAGTGTG
 TGGCAGCACCAGTGTCCCCCTGAGTTCTCTGAGGTGATTAGTTGGAGAAGGAGGTGGCTGGCTCT
 GGATCAAGATCCCAGTGCACAGACTACATTGGCAGCTGTACCTTGAAACACTTCTGTGATGTGCTTGACATGTTAA
 TTCCTACTGGGGAGCCCTGCCAGAGCCCCCTGCGTACCTATGGCTTCTGCCACTGTCCCTCAAAGAAGGAA
 CCTACTCACTGCCAACAGAGCGAATTGTTGTGCCCTGACCTGGAGCTGCCAGTTGGCTCACCACCGGGAACTACC
 GCATAGAGAGCGTCTGAGCAGCAGTGGGAAGCGTCTGGCTGCATCAAGATCGCTGCCTCTAAAGGGCATAT
AGCATGGCATCTGCCACAGCAGAACAGAGCTGGTGTGAGGAAGGTCCCTTCTGTTGTGTTGCCAAGGC
 CAAACTCCACTCTGCCCTTAAATCCCTTCTACAGTGAGTCCACTACCCCTACTGAAAATCATTG
 ACCACTACATTAGGCTGGGCAAGCAGCCCTGACCTAAGGGAGAAATGAGTTGGACAGTTGATAGCCAG
 GGCATCTGCTGGCTGACCACGTTACTCATCCCCGTTAACATTCTCTAAAGAGCCTGTTCATTC
 GTTAAGGAATGGGAAACAGAGTGTGTTAGGACCTGAGAACATCTTATGACTCTCTCTCTCTCT
 TGTCACTAAGTAAAGCGAAGTGAGAGTATTAACTGTTCTCTCCGGCCCCCTGTTACAATGAAGGGC
 AAAAGTATTGCTCTAGTCTATTCCCTCTTAACCTCTGACTAATTGTTATTCTTAGATTGCCAA
 TTAATACTAGGGTGCAGTGTATCCTGGAGAGGTAGGGTGTGTTGGGGAGGAATCCCTGGGGAGATATTAGGAG
 TGCTCTGTTGTTACAAACTCAGGTACCGCAGGGCCTAGCAAGAGACTAAATGACTGATAAGAACCGTGAGAA
 ACATGTTGCTCCAGGCTGATTCGATTTCTGTTTTGGGACGGAGTCTGCTTGTCACCAGGCT
 GGAGTGCAGTGGTGCATCTCACCTACTGCAACCTCCGCCCTGGGTTCAAGCAATTCTCTGCCCTAGCCTC
 CCAAGTAGCTGGACTACAGGCCCTGCCACCACGCCGGCTAATTGTTAGTAAAGATGCTTAC
 CATGTTGCCAGGATGGTCTGATCTTGTGACCTCGTGTGATCCGTCACCTGGCTTGCAAAGCGCTGGATTACA
 GGCATGAGCCACTACACCCAGCCGATTTCTTGTGATCAAAGGATGCTGAGGCTGGCTCCAGTTGGAAATATAATTAGGG
 TGGCAGGGACTGGAGTCAGTGGAGAGTGCAAGCCAGTGTGAAGACAACGGCAGATACTGGCAAAACTC
 GCCTGGTGCAGAGTGAGACTCTGTCAAAAAAAAAGTTCAATGTTACTCCTAGAGAACCCAAAATCCAGA
 TTTGTATATGAAATCTTACCATTTAAAGATTGGCAGCTAATTATTTTAAAGCTGTGAGTGTGATGTG
 TCCCAAACGGACTGGCTCATGGTGGCACGTACAACCTCTGATCTCAGACCGTGCATGCCCTGCTCTTAAG
 ACAACTCCTGTGGCACCGTTCTCCCTCACAGGGCCAAAGCCATAGTGTCCGGTCCAAGGACAAGGCTTIC
 AGTGCTAGGAGAGGTATGAGCAGCCTCTCACCTGTGAGCTGAGGATCACAAGGCTGCCCTGCTCAGTCTGG
 GTCTGTTGGGTGAATGAGGAGATGGAAAGAGGCCCTACCAGCAGCTGTTGGAGCAGGGTCCAAGGAAGA
 GAGGGTGGCCTCGACATCAAACGTGCTGGATTTCTACCAACCCGTTACATCATAACAACTCTGAAACACACA
 CCAGCCCTGAGTTCTGGCTCATTAAGCCTGGAATAGCAATAATCTTTAACTTGCAAAAAAAAAAAAA
 AAA

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FIGURE 14

MOSIMMQAPLLIALGLLLATPAQAHLKPKSQLSSFSWDNCDEGKDPAVIRSLTLEPDPIVVPGNVTLSVVGSTSVP
LSSPLKVDLVLEKEVAGLWIKIPCTDYIGSCTFEHFCDVLDMLIPTGEPCPEPLRTYGLPCHCPFKEGTYSLPKS
EFVVPDLELPSWLTGNYRIESVLSSSGKRLGCIKIAASLKGI

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FIGURE 15

GAAAGATGCGTCCTCGGAGCAGGCAGAGCAGCCAGGCCAGCAAGCTACTCCAGGAAGTGAAAATGTGCTGC
CTCGAGAGCCGCTGATTGCCACGGCAGTGAAGTTCTACAGAATTCCGGTCCGCCAGAGCCCACTTGCAACCA
GGAGAGCATTCAAAGAAAGGGCTGACAGATGAAGAGATTGATATGGCCTTCCAGCAGTCGGGCACTGCTG
CCGATGAGCCTCGCCTGGGCCAGCCACACAGGTGGTCCGTCCAGCCCCCTACCTCATATCTCAGCCAT
ACAGTCCCGCAGGCTCCGATGGCAGATTACGGCCCTGGCCATCATATGGCAGGCATTGCATTGGCTTTC
ACCAGCTCTACAAAGAAATACCTGCTCCCCCTCATCTGGGCCGGCCAGAGGGACAGAAAGCAGCTGGAGAGGATGG
AGGCCGGTCTCTGAGCTGAGTGGCAGCGTGGCCAGACAGTGACTCAGACGACCCTCGCCTCCGTCC
AGGAGCTGCTGATTCAGCAGCAGAGATCCAGGGAGCTGGCCACGAGCTGGCCGTGCCAAGGCCACCA
CCACCAACTGGATCCGGAGCCAGAAATCAACGAACCTCAAGTCCGAAAATTAACCCTTGAAGGGCTTT
TAAATCGGGAGGGCAGGTTCCCTCCATCCCCATCGCCCCGAAGATCCCCCTCCGGCAATCCCAGTCAAGTCA
CACCCCTCCAGCCCTGCGGCCGTGAACCCACACAGCGACGAATCTCACCGTCAAGCAACGAGTCCACGTCGTC
CCTCGCTGGGAAGGGAGGGCCACAGCCCCGGCCAGGGGTCCACGGGTCACCACTTGTCTGGCCCCAGGGAGGA
GCGAGGGGTGGGGACGTCAAGGGCCAGGTGCGGATGGAGGTGCAAGGCGAGGGAGGAAGAGGGAGGA
AGGACGAGGGAGGTGAGGAGGTGAGTGTGAGGCCATGTGGACGAGGAGGTGCCTGGGGGTGCAGAGGGAG
ACCGCCGGGGCCGGGGATGGGGCAGTCAACGAGGACGGGTGGGAAGACGTCGGGCCGGCCAGCAACGA
GTGAGCGGACTAGGGCTGCCCCTGCCTCCAGCCCTCCGGATGGCAATCTAGGTGCCCGTGCGTGGCCAT
CCTGCCTCCCTCTGTGGCCCTGGAGGGCAGTTTGGAGCCAGGTAGGGGGCAAGGTGCCTCCCAGTGCAC
GGCCCTGGGGCAGTGTGGGGAGTCACACTTGTCCACCTGGCCCTTCGCCTGGCCCAGGCCCAGGCCCA
GCCCCAGCCCCAGGGCCAGCTGCCTTTGGCTTTGACTCAAGTCAGGGTGAAGGCAGGAACCCCTGGGGCCAA
GCCCCCTCCCCAGCCCCCTCCCGACAGACGCCCTTGCCCAGGGGTGTTTGTGAGTGTCTGACTACCGGTGACC
ACCACGCAGTGGCCAGAGCTAGCGGTCCCTACGTGCCTCCGACTCAGTGGAGGAAGGTGCGGGTCCCTGTGG
GTCTGCCCATCCCCCTCCCTCCCTGGCCGGCCCTGGACCCGTCAGGGTGCCCCTGTCCCCAGCCCCAAACCCCACTCA
TGCCCCGTCGTCCTCCAGAAACACCGCTGCCGCTCCGAGTGCCCCCGTGTGAATGGTTTCAGCC
TAATCCCCATGGCGAGATGGGGCTATCCGGAGGGAGGCAGGCAGGGCCCTCCGTGACCACAGCCAGTT
TTGTCCCTCCCCCCAGGGAAAAAAATGTTCATTTGTGTGATCATGTTAAGACCTCAGAACGGAAAGATAGGACTGTTA
TATAATTGTTAAAATACCAGTGGCCACCTATTT

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FIGURE 16

MASSEQAEQPSQPSSTPGSENVLPREPLIATAVKFLQNSRVQSPLATRRAFLKKGLTDEEIDMAFQQSGTAAD
EPSSLGPATQVVPVQPPHLISQPYSPAGSRWRDYGALAIIMAGIAFGFHQLYKKYLLPLILGGREDRKQLERMEA
GLSELSGSVAQTVTQLQTTLASVQELLIQQQQKIQELAHELAAKATTSTNWILESQNINELKSEINSLKGLLN
RRQFPPSPSAPKIPSWQIPVKSPSPSSPAAVNHSSSDISPVSNESTSSSPGKEGHSPLEGSTVTYHLLGPQEEGE
GVVDVKGQVRMEVQGEEEKREDKEDEEDEEDDVSHVDEEDCLGVQREDRRGGDGQINEQVEKLRRPEGASNESE
RD

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FIGURE 17A

GCTGTTTGACAACATGGCGGCCATGGTCCGGCCGGCAGTGCCTAAAGGTGGAGAACGAGGAGTA
GAGGAGGCCAGCCAGAGCTGTGAGCAGATCCAGACCTACAGATAAAAACATTATTAATCTATCTGGGATT
TACTCCGGCTTATGATTGAGGGCTTCTCACCTCTGAAGAATGGCTCTGTTGGCAGAGATTGGGTTTAT
GCCTCTCTGAAAAGACAGCTAAATGGTGGGCCAGATGTCATCAAGTGGAAAGGAGAGTAATTCCGGATGT
ACCAGAACGATCTACAGTGCCACGGAAAGTGGACAAAAGAGTATACATTGCAGACAAGAAAGGATGTTGAGAAA
TGGTGGCATCAACGAATAAAAGAACAGGCCCTCCAAAATTTCAGAAGCTGATAATCGAAGGCCAAATTTCAGTG
CTTCCATGTTCCCTTATCCCTCTGGTAAGCTGCACATGGCCATGTGCGTGTACACCATCAGCAGACCCATA
GCACGGTCCAGAAGATGAGAGGGATGCAGGTATCAACCCATGGGATGGGATGCTTGGATTGCTGCTGAA
AATGCCAGTCGAGAGGAATCTACATCCACAAAGTTGGACACAAAGTAATATTAAACACATGAGGAAACAGCTT
GATCGTCTGGGCCTGTGTTCTAGCTGGGATAGGAAATAACTACGTGTTGCCAGATTACTACAAGTGGACTCAG
TATCTCTTATTAAACTGTATGAGGCTGGCTGGCCTATCAAAGGAGGCCCTGGTTACTGGGACCAGTGGAT
CAAACAGTGTGCCAATGAGCAGGTGGATGAACATGGCTGTTATGGCCTCTGGAGCAAAGGTGGACAGAA
TACCTCAGACAATGGTTATTAAAGACAACCGCTTATGCAAAGGCCATGCAGGACGCGTGGCAGACCTCCAGAA
TGGTATGGAATAAAAGGCATGCAAGCCCAGTGGATTGGGACTGTGIGGGCTGCCACCTGGACTTCACATTAAAG
GTTCATGGGCAAGCCACGGCGAAAAGCTGACTGCCATACGCCACCCCTGAAGCCATTATGGCACCTCCCAC
GTGGCCATCTGCCAGGCCACAGACTCCTACATGGGACAGCCTCTGAAGGAAGCCTTGAGGATGGCCCTTGTC
CCTGGCAAAGATTGCCCTACGCCGTAAATGGCTGTGAACATGCTTACCCAGCAGGAGGTCCCTGCGTTATTG
GCCAAAGCTGACTTGAAGGCTCTGGATTCAAATAGGAATTCCAGTACTAGCTCAGAGGACACCATCTTA
GCCCAAACCTGGCCTGGCCTACTCTGAAGTCATTGAAACACTTGCCTAGGCCACCCCTGAAGCCATTATGGCACCTCCCAC
GCTGAGTTCACAGGTATGACCCGGCAGGATGCTTCTAGCCCTGACTCAGAAAGCCGGGGAGAGAGTGGGT
GGAGACGTGACAAGTATAACTGAAAGACTGGCTGATTCACGGCAGCGGTACTGGGACACCAAATCCCCATT
GTCCACTGCCAGTGTGGCCCCACACCTGTGGCCCTGGAGGACTTGCCTGTGACCCCTGCCAACATCGCGTCT
TTCACTGGCAAGGGAGGCCACTGGCATGGCTTCAGAGTGGTGAACTGCTCTGCCAAGGTGCAAGGG
GCAGCCAAGAGAGAGACAGACGATGGATACCTTGTGATTCTGCTGGTACTACTTCAGATACTGACCC
CATAATCCACACAGCCCTTTAACACACAGCAGTGGCGATTACTGGATGCCGTGGATTGTACATTGGAGGGAA
GAACATGCCGTATGCACTTGTCTATGCAAGATTCTTAGTCATTGGCATGATCAAATGGTAAACAT
AGGGAGCCTTTCAAGCTGCTGCCAAGGCCCTATCAAGGGCAGACATTGCCCTACCATCTGGACAGTAT
CTACAGAGAGAGGAAGTGGATCTCACAGGTTCCCTGTTCATGCAAAACGAAAGAGAAGTTAGAGGTGACG
TGGGAGAAGATGAGTAAGTCAAACACAACGGGTGGACCCAGAGGAAGTGTGGAGCAGTATGGGATCGACAG
ATTGGCTCTACATCCTTTGCTGCCCTCTGAGAAGGATATCTGTGGATGTGAAACTGATGCTCTCCCT
GGGGTGTGAGATGGCAACACAGACTGTGGACCTTGACAACCTCGGTTATTGAGGCCAGGGCTCTGGGAAGTCT
CCCCAGCCTCAGCTGCTGAGTAACAAGGAGAAAGCTGAGGCCAGGAAGCTGGGAGTACAAGAACCTCCGTAC
TCTCAGGTGACCACCAATTACAGAGGACTCTCACTGAATTCTGCAATTCTCAGCTGATGGACTCAGCAAT
GCCCTCTCGCAAGCCTCTCAGAGCGTATTCTCACAGGCCAGTTGAGGATGCTTGCTGCCCTGATGGTA
ATGGCTGCTCCACTGGCCCTCATGTAACCTCAGAGATCTGGCAGGCCCTGGCCTGGTGCGAGGAAGCTCTGT
GCCCACTACACTTGGGATGCCAGTGTGCTGCCAGGCATGCCCTGCTGTGGACCCGGAGTCTGCAAGCAGC
GAGGTTGTCAGATGGCAGTTCTGATCAACAATAAGCTTGTGGCAAATTCCTGTGCCCAACAAAGTTGCCGG
GACCAGGACAAGTCCACGAATTGTTCTCAAAGCAGCTGGGTGTCAGGCTTGTGCAAGGAGCAAGCATCAAG
AAAGTCCCTCTTCCCCGAGAACTGCCCTCATCAACTTCTGGTCAAGAT**TGA**CAGCCAGGAGGCTGAGCTAC
CACGAGGGCCTCTGAGGAACCTCCTCCAGGCCCTGGGATGAGGGGGCGATGCTGCTGCCAGGGAAAGGGAAA
AGACAAATGTCTGACTGTTGACCTGGCTCTGTCAGACTGCAGTCACAGTGTGCCCTGTAGTGTGGCT
GTGCTGGGGTGAAGGTGAGCTGGCAGGAGAAATATGAGCTACTGAGGAGGGGTTGGACATCCTGCCCTCA
CCCCCCCACCCACACTGCAGGTAGAGGAGGCCATCTGATCCCATGGGAGGCCATCAGAGACACTGCTGGTGGAGC
AGGAAGGAGCAGTGCCCTCGAGCAGGCCAGGAAGCCTGCGGATCTGGGAAATGGCTCTGCCCTAGGCAC
GGAATTGAGGCCAGCCTGAGGAACCTCAGGACTCAGGTGCAATGTGCCAGCCACTGGAACTGCTAAGTGGCC
TCCAGATGGTAGTGAATGGCTCTTGCCTCAGGCTGGATGAGGAAGTCATTAGGAAATGTTCAAATAACCAA
TATGTGGAAATGGACACAGGGATCTCTGAAGTGTGTTGAATCAAAGGCAGGCAGTGTGGCTCTGCCCTG
TGTCCCCACCACTCCCCAGCTGTCATGCAGGCCCTGCTGCCCTCCCCAACCCAGCTGGATGTGCCCTCCAGGCC

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FIGURE 17B

CTGTGGTTCTGACACACAGGATCCCAGGCAAGGCACCACTTCCTCACATGAATGAGGAGCAGCAAGTCATAACCA
CTCCCTGGGTATAACAATTGCTGTGTAGTGAAGTGGAACCGAGGCTCAGGCTGCTGGTCCAACCTCAGAGCCCC
ACCGCAGCCCAGTAGGGATGCAGCACGCCAGAGGGCTCATGTGGGCCAGATGGCAATGCCACCATTGTTGA
TGTGACTCCAGAGCCAGTTATTAGGAAGAGCAAGCTCACCAAGAGGGACTGGAACGTGAGGCCAGATGTTGC
CTCCGGTGTCCAAGCCACAGCGGTCTGGCTGTTGGAAAGATGGCCAGGAATGGACTCATACCAATTGGCACATTAG
GCTAATCTGGTTTATGTGAAGTCAGCAATTAAAGTGTCCACTAGAACTGACCTAAGCCACTGATTAATATTT
AATGAGGGAAGGTAGGGGAGAATCTAGCCATTTATAATGCCAGAAATCTATATATGTTATCTGATGCCATT
CTGAAGTAGCCTCACATGTGGTCCCCCTGCAGTTCAACAGATGACTTTTTAGTGTAAATAAAATGTT
ATCATCTATG

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FIGURE 18

MASVWQRLGFYASLLKRQLNGGPDVIKWERRVIPGCTRSIYSATGWTKEYTLQTRKDVEKWWHQRIKEQASKIS
EADKSKPKFYVLSMFPYP SGKLHMGHVRVYTISDTIARFQKMRGMQVINPMGWDAGFLPAENAVERNLHPQSWT
QSNIKHMRKQLDRLGLCF SWDREITTCLPDYYKWTQYLFIKLYEAGLAYQKEALVNWDPVQTVLANEQVDEHGC
SWRSGAKVEQKYLROWFIKTTAYAKAMQDALADLPEWYGIKGMOAHWIGDCVGCHLDFTLKVHGQATGEKLTAYT
ATPEAIYGTSHVAISPSHRLLGHSSLKEALRMA LVPKGKDCLTPVMAVNMLTQQEVPVVILAKADLEGSLDSKIG
IPSTSSEDTILAQTGLAYSEVIETLPDGTERLSSSAEFTGMTRQDAFLALTQKARGKRVGGDVTSDKLKDWLIS
RQRYWGTPIPIVHCPVCGPTPVPLEDPVTLPNIASFTGKGGPPLAMASEWVNCSPRCKGAAKRETDMDTFVD
SAWYYFRYTDPHNPSPFNTAVADYWMPVDLYIGGKEHAVMHLFYARFSSHFCHDQKMKVKHREPFHKLLAQGLIK
GQTFRLP SGQYLQREEVDLTGSVPVHAKTKEKLEVTEKMSKS KHNGVDPEEVVEQYGDITIRLYILFAAPPEKD
ILWDVKTDALPGVLRWQQLWLTTRFIEARASGKSPQPQLSNKEKAARKLWEYKNSVISQVTTHFTEDFSLN
SAISQLMGLSNALSQASQSVILHSPEFEDALCALMVMAAPLAPHVTSEIWAGLALVPRKLCAHYTWDASVLLQAW
PAVDPEFLQQPEVVQMAVLINNKACGKIPVPQQVAR DQDKVHEFVLQSELGVRLLQGRSIKKSFLSPRTALINFL
VQD

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FIGURE 19

TATATTGGCAGTTATTGAGGGTAAAGCAATATGTAAACAGAATGTATAAATTTTGATAAAACAGTCTATA
TTTATTAAAAAATGAATTATAACCCATTTCAGTTGCCTGCATCATAGAGTGGACACTCCATTGCTTCTT
TCCGGCCACACTGCTACAATCCAGCACTAACTATCCATGTCAGGGTAAGGATCGAGATCGAGAACCCACACT
GCCAGTGAAGAGCTACGTCTTACTGCATAAATTAGAGGAAGCAATTGGAACAACGGAACCTCAAACACTATA
AATACTGAATTATCGAACACTGCCAGGCACCTCAGCAGAAGACAAGGAAACTGAAGAAGCTTTAGATGAGGA
ATTCCTCACTATGATCCCTGCTGCGCAGATGCAATTCAACAAACCTCTCAAGAAAATTGAAGCAGTGTG
CCACAAACTATATGGTGGTCAAGAAGCAAGAACATCAGACACCCCTGACCTGAAACATACGTGCTGGTACAC
ACCTCTGCTGGTGCTTATCTCTGGATAGTTACAGCAGTCCAACCCCTGGAATCAACACCTTCTCAGGTGT
AGCCAACCAAATCCACACTCTGTGAAAGGCCACATATGGAGAAGTAAAGGATGGTCTTGGATGAAAAAG
ACAACACAAGTGCCAGGCCACAAAGTGGCCCAGGCCAGGAACGAATCTCTCAGGCTGCATCAGGATGAATGA
TGACCCAAGTATGGAAGAGAATGGTGTGAAACGCGTGTCTGAGAGCCTGCTGCAGTCCAGGGATATTCTC
ACTACCATTACCCAGACACACTTCATCGACAGACGGTACTATAACTCAAGTGTCTGGATTAGAAATTCTGAA
TATGGCTCTTGACCTTGACAGAAACTCGCTCTGTAAGAAAAGAGGAGGATACAAGATCAGCTCTCCACGAT
AGAGGCCAAGGCACAAGTCCAGCTCATGATAATATTGCAATTCCAAGACTCTACGAGTAAGGATAAAACCATATT
AAATCTGGAAGCCAAGAGGAACCAAGAACATAGAAGAACATAAAAAGAACATGCTCAGGAGACTCTGTGGT
TTCCCCTCTCCTGTAACCACTGTGAAATCGGTTAACGTTAGACAAAGTGGAGAACACTCTGCTAATGAGAAGGA
GGTGGAGGCAGAATTCTCAGATTATCTTGGGATTAAAGTGTGACTGGTTACCTTGGAGAACAGAGTGAAGCT
TGAAGAGAGGTCCCGTGAACGGCAGAAGAAAATTGAAGAAAGAACACTAACTCTTAAACTATTAGAGTC
TTAACACCTCTGTTGAAGATGACAACCAGGCACAGGAAATCATTAAGAAGCTGGAGAACAGTATAAAGTTCT
TAGCCAGTGTGCAGCACGAGTGGCCAGTAGGGCTGAGATGTTGGGAGCCATCAATCAGGAAGCCGGTTAGTAA
AGCAGTTGAAGTGTGATTCAAGCACGTAGAAAACCTGAAAGAGGATGTATGCCAAAGAGCACGCTGAATTAGAAGA
ACTGAAACAGGTTCTCTGCAATGAAAGGTCTTCAATCCTCTGAAAGATGATGATGACTGCCAAATTAAAAAA
ACGTTCAAGCTCTCTAAACTCCAAGCCATCTCTACGAAGAGTGACTATTGCCCTTTACCCAGAAATATTGG
AAATGCAGGAATGGTGGCTGGATGGAAAATAATGATCGATTCAAGGTCAAGCAGTGGCGTATTTGGG
GTCAAAGCAGAGTGAACACCGTCCCTCATTACCTCGATTATTAGCACCTATTCTGGCAGATGCTGAAGAAGA
AAAATGTGAACAAAAACTAAAGATGACTCAGAGCCATCTGGAGAACAGTAGAAAGGACAAGGAAGCCAAG
TCTTCTGAAAAGAAAATAATCCATCAAAGTGGATGTCTCTCAGTTATGACACAATAGCTTCTGGCAAC
AAATCTCAAGTCTCCATCAGAAAGGCTAATAAGGCCCTGGCTCTATTGCAATTGACTGTGAGCT
TTGATGAGCTCTCACAGGCCATTATTCCAGAACGACTCTGAGATGCCCTCCACACAGCAAGAGGACTCATG
GACGTCTCTAGAACATATCTGTGGCATTACAGACTCCGACACAATGGGCCACCACAGTTGACAGCAGGA
CATCCTAATATATGGATCTGATTTAAGTTCACTGAACTTCTGAAATTAGTAACCTTGTAGCTGGAAA
GTATAGCATGAAACCAGAGGTTCTCAGAATGACCGTAAGATAGCTTACATTCTCTTTGCCTTATCTCCCC
AACTAAAATACAATGGG

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FIGURE 20

MESTPFSGVANQIHTLCERPTYGEVKDGALDVKRQHKCPGPTSGPSPGTNLSGCIRMNDDP SMEENGVERVCPE
LLQSRGYSSLPLPRHTSSTDGTITSSDPGLEILNMASCDLDRNSLCKKEEDTRSASPTIEAQGTSPAHDNIAFQD
STSKDKTILNLEAKEEPETIEHKKEHASGDSVSVSPLPVTTVKS VNRQSENTSANEKEVEAEFLRLSLGFKCDW
FTLEKRVKLEERSRDWAEENLKKEITNSLKLLESLTPLCEDDNQAQEIIKKLEKSIKFLSQCAARVASRAEMLGA
INQESRVSKAVEVMIQHVENLKRMYAKEHAELEELKQVLLQNERSFNPLEDDDDCQIKKRSASLNSKPSSLRRVT
IASLPRNIGNAGMVAGMENNDRFSRRSSSWRILGSKQSEHRPSLPRFISTYSWADAEEEKCELKTKDDSEPSGEE
TVERTRKPSLSEKNNNPSKWDVSSVYDTIASWATNLKSIRKANKALWLSIAFIVLFAALMSFLTGQLFQKSVDA
APTQQEDSWTSLEHILWPFTRLRHNGPPP

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FIGURE 21

ATGGTGTGTGCCCGGTATTGGGAAGCTGCTGCACAAGCGCGTGGTGTGCCAGCGCCTCCCCACGCCGTCA
GAGATCCTCAGCAACCGCGGTCTCAGGTTGAGGTGGTCCCCCTCAAGTTAAAGAGAACGCTGGACAAAGCCTCC
TTCGCTACTCCGTATGGGTACGCCATGGAGACCGCCAAGCAGAAGGCCCTGGAGGTGGCAACCGGCTATACCAG
AAAGACCTGCGGCCCGACGTGGTATTGGAGCGGACACGATCGTACGGTCGGGGCTGATTCTGGAGAAC
CCGGTGGACAAGCAGGACGCCAACAGGATGCTGTCCGGTTGAGTGGAGAGAACACAGCGTGTACAGGTGTC
GCGATCGCCACTGCTCCAGCAAAGACCATCAGCTGGACACCAGGGTCTCGGAATTCTACGAGGAAACGAAGGTG
AAGTTCTCGGAGCTGTCCGAGGAGCTGCTCTGGAAATACGTCACAGCGGGGAGGCCATGGACAAAGCTGGCGG
TACGGTATCCAGGCCCTGGCGCATGCTGGTGGAGTCCGTACACGGGGACTTCTGAACGTGGTGGGATTCCCG
CTGAACCACTTCTGCAAGCAGCTGGTGAAGCTACTACCCGCCGTCGGAGGACCTGCGCGGAGTGTCAAG
CACGACTCCATCCCGGCCGACACCTCGAAGACCTCAGTGACGTGGAGGGGGCGCTGGAGGCCACTCAG
AGGGACGCGGGCAGCCCGATGAGAAGGCCGAGGGGGAGAGGCCACAGGCCACGGCAGAGGCTGAGTGTAC
AGGACTCGGGAGACCTGCCTCCGACACGCCCTGGAGCTGATTGAGGGTTATGCTATCCAAGGGC
CTGCTACCGCTTGCAAAGGTGTTGATTATTAAAAGATGAAGCACCCCAGAAGGCTGCGGATATTGCC
AGCAAAGTGGACGCCTCTGCGTGTGGAAATGGAGAGGGCTCTGGACATCTGCTGCCATGGGCTCTGGAGAAC
ACAGAGCAAGGTTACAGTAACACAGAGACAGCGAACGTCTACCTGGCATGGATGGCAATACTCTGCACGGC
TTCATCATGCACAATAATGACCTCACATGGAACCTTTACATACCTGGAGTTGCCATCCGAGAGGGAACAAAC
CAGCACACAGGGCTTGGGAAGAAGGCCAGAGATCTGTTCCAGGATGCGTACTACCAGAGGCCGGAGACGCC
CTGAGGTTCATGCGGCCATGCACGGCATGACGAAGCTGACTGCGTGCAGGTGGCACGCCCTCAATCTGTCC
CGCTTCTCCCGCCTGCGACGTGGGAGGCTGCACGGGTGCACTGGCCGAGAGCTGGCCCGTGAGTACCCCTGT
ATGCAGGTGACTGTGTTGACCTCCCAGACATTATCGAGCTGGCCGCCACTTCCAACCCCCGGACCGCAGGCA
GTGCAGATCCACTTCGACAGGTGACTTTCAAGGACCCCTCCCGCAGCGCTGAGCTGTACGTCTGTGCCGG
ATCCTGCATGACTGCCAGACGACAAGTCCACAAGTTACTCAGCAAGGTGCCAGAGAGCTGCAAGCCAGGGCC
GGCCTGCTGCTGGTGGAGACGCTCCTGGATGAGGAGAACAGGGTGGCGCAGCGCAGGCCCTGATGCAGTC
ATGCTGGTGCAGACTGAAGGCAAGGAGCGGAGCCTGGCGAGTATCAGTGCTGGAGCTGCACGGCTTCCAC
CAGGTGCAGGTGGTGCACTTGGGGGTGTCCTGGATGCCATTTGCCACAAAGTGGCCCCCTGAAGGCCAGGCA
GCATGTTCATTATAG

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FIGURE 22

MVLCPVIGKLLHKRVVLASASPRRQEILSNAGLRFEVVP SKFKEKLDKASFATPYGYAMETAKQKALEVANRLYQ
KDLRAPDVVIGADTIVTGGILEKPVDKQDAYRMLSRLSGREHSVFTGVAIVHCSSKDQOLDTRVSEFYEETKV
KFSELSSEELLWEYVHSGEPMKDAGGYGIQALGGMLVESVHGDFLNVVGFPPLNHFCQLVKLYYPPRPEDLRRSVK
HDSIPAADTFEDLSDVEGGGSEPTQRDAGSRDEKAAGEAGQATAEAECHRTRETILPPFPTRLLELIEGFMLSKG
LLTACKLKVF DLLKDEAPQKAADIASKVDASACGMERLLDICAAMGLLEKTEQGYSNTETANVYLASDGEYSLHG
FIMHNNDLTWNLFITLEFAIREGTNQHHRALGKKAEDLFQDAYQSPETRLRFMRAMHGMTKLTACQVATAFNLS
RFSSACDVGGCTGALAREYPRMQVTVDLDPITIELAAHFQPPGPQAVQIHFAAGDFFRDPLPSAELYVLCR
ILHDWPDDKVHKLLSKVAESCKPGAGLILVETLLDEEKRVAQRALMOSLNMLVOTEKGERSILGEYQCLLELHGFH
QVQVVHLGGVLDAILPPKWPPEAQACSL

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FIGURE 23

CGCCTCTCCAAAGTCTAGCCGGCAGGGGAACGCGGTGCATTCTGACCGGCACCTGGCGAGGCTATCGTCC
CGTGAGGGCGGTTCTCGAGCCTGGGGCGCTCAGATTGCTTGGAGACGCTGAGAGAACCTTGCAGAGCGCC
GGTTGACGTGCGGAGTGCGGGGCTCCGGGGACTGAGCAGCACGAGACCCCCTCCCTCCGGGTTTCACAC
TGGCGAAGGGAGGACTCCTGAGCTCTGCCTCTTCAGTAACATTGAGGATTACTGTGTTTGTGAGAGCTCGCT
AGGCGCCCTAAAGCAACAGAGTCTGAGAAATCGAGAAACATGATAAGGAATTGGCTGACTATTTTATCCTTTT
CCCCTGAAGCTCGTAGAGAAATGTGAGTCAAGCGTCAGCCTACTGTTCTCCTGCTAAAGCTGGAGAACGGC
AGCTGACCAACGTCAGCCTCACCTGCGGCCACCATTAATGCAACCCCTGGTATCAGTTGAAATCACATT
CGTTCCAAAATATTACTATCCTGAGCTCCCGATGAAGTTGTGGTGCTCCTGGAGTGACAAACTCCTTTT
CAAGTGACATCTAAAATGTTGGACAACTTACTGTTATCTACATGGAAATCACTCCAATCAGACCGGGCCGAGG
ATACGCTTCTGTGATCCGACAGCGCCATTAGCATCATAAACCAGGTGATTGGCTGGATCTACTTGTGGCC
TGGTCCATCTCCTCTACCCCTCAGGTGATCATGAATTGGAGGCGGAAAGTGTCAATTGGCTGAGCTTCGACTTC
GTGGCTCTGAACCTGACAGGCTCGTGGCCTACAGTGTATTCAACATCGGCCCTCTGGTGCCTACATCAAG
GAGCAGTTCTCCTCAAATACCCCAACGGAGTGAACCCCGTGAACAGCAACGACGTCTTCAGCCTGCACGCG
GTTGTCCTCACGCTGATCATCATCGTGCAGTGTGCCTGTATGAGCGGGTGGCCAGCGCGTGCCTGGCCTGCC
ATCGGCTCCTGGTGTGCGTGGCTCTCGCATTTGTCACCATGATCGTGGCTGCAGTGGAGTGATCACGTGG
CTGCAGTTCTCTGCTTCCTACATCAAGCTCGCAGTGCCTGGTCAAGTATTTCCACAGGCCTACATG
AACTTTACTACAAAAGCACTGAGGGCTGGAGCATTGGCAACGTGCTCTGGACTTCACCGGGGGCAGCTCAGC
CTCCTGCAGATGTTCTCAGTCCTACAACAACGACCAGTGGACGCTGATCTCGGAGACCCAACAAAGTTGG
CTCGGGGTCTTCTCCATCGTCTCGACGTCGTCTTCTCATCCAGCACCTCTGTTGACAGAAAGAGACCGGGG
TATGACCAGCTGAACTAGCACCCAGGGACCCAGTGTACCCAGCCTCTGGCCTCGTGCCTGCTGGGAAGGCCTC
ACCCAGCGAAGGCCGGAGAAGCGGTTGGCCCTGGCACACAGGGCTGGCTCAGTGTGGACAGAGGAGACCACT
CTGCTCTGGGCCAGAGGCCATTCAATAGCCTGCCCTCGTCCGGGCCCTCTGGCCTCCCCGGCCAGGCACG
TGGCACCGTCGCCTGACACCGCCATCTTTCTTAAGGCTTCAGGCAGCGCACAGGCTCTGGCAGCCGTC
TCAGGCAGGACTGGCACCAAGCTGCGCCAGGCTTGGCCCAAACCTACCAAGCGTTCTGCAAGCAGCTGA
AGGGCTGACCTTGAGCCGGGTGAGCCAAGGGACTTGTGCCACCGCTGCATTCCAGAGATCAAGCAGCCCG
GTGCCGTGGCCAGTGAACTCAGAGGTGCTGGACGGCTAGGACTTGGGTTAGGCCATGGGCTTTCT
TGAAGGCCACTTCTGACGTACTCTGTACATAACTCAGCGTCCGTGACTGCAGTAACAGCCAGGCCCTACCCA
GAGTATTCTGAGCCATGAGGGCCACCAAGATTGGTCTGAATTGGATTCTGCCAGCGCATTAGCATAGTAA
CTCCTTCAGATTGGAGGGACGTTGGAAGTGGCTTACTCTCTGCCCTCTCCACCTCACCTTCT
CAGATGAGCCCATCTGAGCACATCCAGCTGCCCTACCCAGCATCTGGAGTACAGGACATAGCTCTCCCTGC
TACCAAGCTGCTGCCCTAGAGGTCGTTAGGCCTGCCAACGGGACCCAGCTCCCTGGAGCGAGGGCAGGCCCT
CCCTCTCTCCCCAGACACCTACTTGAGACTCACCAATTCTGGCCTGTCAGGAGCCTCAGATAAGTATTG
ACTTGAGACCACCTCACACAATCTGTATGGGCCAACCCCTGATCTCAAACCTCCTCCCTGCCAAAGCTGTC
CTTCCTATGGCAGGAGGGTGGGGTCCCAGGACGTGCCATACATGACTTGAGCTGTCAGTCCACTGAGTT
CCTCTACGAGATCAACGCGAGGGCCTGTATCTGAATTAAAGCCTACTCGCTTCTTC

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FIGURE 24

MIRNWLTIFILFPLKLVEKCESSVSLTVPPVVKLENGSSTNVSLTLRPPLNATLVITFEITFRSKNITILELPDE
VVVPPGVTNSSFQVTSQNVGQLTVYLHGNHSNQTGPRIRFLVIRSSAISIINQVIGWIYFVAWSISFYPQVIMNW
RRKSVIGLSFDFVALNLTGFAVSVFNIIGLLWVPYIKEQFLLKYPNGVNPVNSNDVFFSLHAVVLTLLIVQCCL
YERGGQRVSWPAIGFLVLAFLFAFVTMIVAAVGVITWLQFLFCFSYIKLAVTLVKYFPQAYMFYYKSTEGWSIG
NVLLDFTGGSFSLQMFLQSYNNNDQWTLIFGDPTKFLGVFSIVFDVFFFQHFCLYRKRPGYDQLN

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FIGURE 25

CTTACAACCTCGCGCGGCCCTGGCCCCCTGCGCCGCCGCCACAACAAAACAGCGCAGCGCTCCGGCGC
CCGGTTCAGAGCGACCTGCGGCTCAGAGCGGAGGGAGACTGACCGGAGCGCGATCGGGACAGCGGCCGGACA
GCGCGAGACGCGCGTGTGTGAGCGCGGACCAAGCGGGCCAGAAGCGGGCTCGCAGCCAGAGGGCACCT
CTGCAAACATGTCTGTGGATCCCTATCCAGCAAAGCTAAAGATCAAGCGAGAGCTGAGCGAGAACACGCCGC
ACCTGTGGACGAGGCCTGATGGGCTGCGGTGCGAGCTGAACCGCATCTGCGCGGGCTCCGCCGAGG
AGGTGACACGGCTCAAGCAGCGCGCCGCACACTCAAAACCGTGGCTACGCCGCAGCTGCCGTGAAGCGCG
TGTGCCAGAAGGAGGAGCTGAGAAGCAGAAGTGGAGCTGGAGCGCAGGGTGGACAAGCTGGCGCGAGAACG
CCGCCATGCCCTGGAGCTGACGCCGTGCCGCCAGTGCAGGGCCTGCAGGGCTCGCGCGCTCCGTGGCG
CCGCCCGGGCCGCCACGCTCGTGGCGCCAGCGTACCATCGTCAAGTCCACCCGGCTCGGGGT
CTGGCCCCGCCACGGCCGGACCCCGCCACGGCCCGGCCCTGCTCCTAAGTGCCCGCCCCGCCATGCCCTCA
GCCACGCCCTCCGCCCTCAGCTCCCTCCCCAAAGTGCCTGAGCGCCGCCTGTGCCCAGGTCCCATTCTCTG
CAGCACTGGCCCTGGTGCACACACATTCCCTCGTGGGCCCTGTCTCCTCTTGCAAGCCCCCAAACGGGAC
CGAATGACCTGGGAAGGGAAAGTTGGTAGGTTGGGATGGGCAGAGGTCTGGATCTGGGATGCCCTGGCT
GAAAGTTAGCCTTTAGATTGAGAGATAACAGAGCCGGCTAGAGAACAGCTGTGGGGAGAACAGGGCACCC
CTCATCTGAAACTGCTCTTATTGICCAATATGCCCTCCAAACCTCCCAAGGATTCAAAGCTAGGTTGGCTG
TCTGTGACTTACGGGACCGTCTGCTGAGAAATTGCACTGAAGAGATGCCCTCCTGGTTGGGCTGGGCT
GCCTGGCCTCCGAAACTAAAGAGTGGTGGGAAGACTAGTGAAACCCAGTTACGGATGGGAAACAGGCCTG
AGGTACACATTCACCTAGTGGTTGTGTTGGACCAAAACCTGGGTGTCTCACTGCTGAGTCCAGCCATGGTTT
CAGGGGACAGTGGACAGGGACTCAGAAATGTGGGGAGGGCCTCCCTGGCTGGAGACCCTCTGCAAGG
GAGGGGAGAGAACAGCAGAGGGAGAGAGAACGGTGACACGGATGGAAGAGTGGGAAGGGCTGGCTCAGCCC
TAGGCTGCCCTGCAGCCAGGGTGTCCCCGGGCTGGCCAGTCAGAGAACGGGGCATGGACTGCTGGCAAAT
AGGGAGACAAGGAGACAGACCCCTGCAGTCCTACTACAGTCTGGAGTGGGCTCTAAGAAGAACGGTCCACCTCA
ACCCCTGTCAGTGTCCACTGTGGGTGGGGCTGACCCCTGCCCTTGATTGTCATTCTCTGGGAAGCCCAGTCT
CAGTCCCTCCCCAACACTGTCCACACTGCCCTCCCACTGTTATTGACGGATCTAAGTTATTCTCC
CAGCCAGAGCCCGAGCTCTGCCCTGGAAAAGTGGCGTATGCCCTGAGCTGGCTTATATTATATCTG
CAAATAAATCACATTTATCTTATTAGGGAAAGCCGGAGAGCAACAAACAAAAATGTTAAGCCGGCGCG
TGGCTCACATCTGTAATCCAGCACTTGGGAGTCCAAGGAGGGGATCGCTTGAGTCCAGGAGTTGAGACAG
CCTGGACAACATGGTGAACCCCGTCTACAAAAAAATACAAAAAATTAGCCATGCATGGTGCTCATGCCCTG
TCCCAGCTACTTGGGAGGCTGAGGCAGGAGGATCACTTAAGCCCAGAAGGCAGAGGTTGAGTGA
CACCACTGCACTCCAGCCTGGCAACATAGCAAACATCTGCTCAAAAAAAAGTTAAAAAATTGCCCGGCTC
CTAGAATTATTATTCCTGACTTACAGCAAGCGAGTTACGTCTCTGTTAGACTTCTAAATAAAG
TCAAATTCTTCTTTCCACAGAAAAAA

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FIGURE 26

MSVDPPLSSKALKIKRELSENTPHLSDEALMGLSVRELNRHLRGLSAEEVTRLKQRRRTLKNRGYAASCRVKRVCQ
KEELQKQKSELEREVDKLARENAAMRLELDALRGKCEALQGFARSVAARGPATLVAPASVITIVKSTPGSGSGP
AHGPDPAHGPASCS

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FIGURE 27

GC GGAGCGCGCTCCCAGCGAAAGCAGCAGGGCAGGGATCTCGTTGGAGGAAGGGACTGCTCTGGTGTAGA **A**
T GCTGTGCGTCGGAAGGCTGGCGCTTGGAGGCCAGAGCAGCAGCTCTGCCGCCCGCCGGCGGGCGGGAA
GCCTCGAAGCCGGGATCCGGGCCGAAGGGTCAAGCACCAGCTGGTCTCCGTGGCGCCGCTTCAATGTCAAGC
CCCAGGGCAGCCGCTTGGACCTGTTCGCGAGCAGGGCGCTTTTGAGTTCTGAGCTGAGTGCCTGAGTGC
GATTTCATATTGCACAAGAAAAGCCTTGAGAAAGACAGAATTGCTTGAGGACCGTGCATGTCACCCACCTG
GGCCCCAGACCGTGTGATCTCGATGAGCTCTGGATTCTTATGCAGAGTGGCCGACTGGCTGATTGTGA
AAATCGCTCACCTGAGCCAGCATTAGAGAAGCTGCGGAAGAAGCTTGTAGAAGTATTGGCACCATGGTAGAGA
AGTTGAACACAAAATGTGGATTATATCAAAGTTGCAAAAATTACTAGCTGATAAAAATCTGTGGATTCCCTG
ATCCAGAAACAAGGGAGTGGCTGAACGTGTTATGTTGATTGAAATTAGTGAATCCATCTAGACAAACAAA
AGCGTAAAAGAGCAGTGGACCTCAATGTTAAATCTGGATTGAGTAGTACATTCTATGGAACCAATTTC
CCAACAAAGATTGAGAACGATCTTACCAAGAACACATTGTCGTAACCTTACATCTGCTGGGATCATCATAA
TTGATGGTCTCACCGAGAACATCACCAGATGACTGGTGCAGAGCTGCTTATAAAATTCTTATCCCAATG
CTGGTCAATTGAAATGTTAGAAGAATTGCTCAGCAGCAGAGATCTCTGGCAAAGTTGGGGTATTCCACGT
TTTCTCACAGGGCTCTCCAAGGAACGATAGCTAAAATCCAGAGACTGTCATGCACTTCTGAAAATCTG
ACAAAATTCTGAAAGAACTCTGAAAGATTGAGATGATACGAGGGATGAAAATGAAACTGAATGCTAAAATT
CCGAAGTAATGCCCTGGGACCCCCCTACTACAGTGGTGTATTGTCAGAAAGGTATAATTGAGCCCAGCC
TATATTGCCGTTTCTCTTGGAGCATGCATGGAAGGCCTGAATATTGCTTAACAGACTGTTGGGATT
CATTATATGCAGAGCAGCCTGCAAAAGGAGAGGTGTGGAGCGAAGATGTCGAAAATGGCTGTTCATGAAT
CTGAAGGATTGTTGGGGTACATTACTGATTTTCAAGCAGACAAACACATCAGGATTGCCATTCA
CTATCCGTGGAGGCAGACTAAAGGAACATGGAGACTATCAACTCCACTTGTAGTTCTATGCTGAATCTCCCC
GTTCTCAAGGAGTTCTCAACTTGTCAACTCCTGGCATGATGGAAAATCTTCCATGAAATGGACATGCCA
TGCATTCAATGCTAGGACGTACTCGTACCAACACGTCACTGGACCAGGTGCCACTGATTGCTGAGGTT
CTTCTATTCTGATGGAGTACTTGCAAAATGATTATCGAGTAGTTACCAATTGCCAGACATTACAGACTGGAC
AGCCACTGCCAAAAATATGGTGTCTCGTCTTGATGAACTAAAGGTTGTGCTGCAGCTGATATGCAACTTC
AGGTCTTTATGCCACTCTGGATCAAATCTACCATGGGAAGCATCCCTGAGGAATTCAACCCACAGACATTCTCA
AGGAAACACAAGAGAAATTCTATGCCCTACCATATGTTCAAATACTGCCCTGGCAGCTGCGATTGCCACCTCG
TGGGGTATGGTGTAGATATTACTCTTACCTCATGTCAGAGCGGTGCCCTCATGGTTGGAAGGAGTGT
TACAGGATCTTCAACAGGGCTGCCGGGAGCGCTATGCAAGGGAGATGCTGGCCACGGTGGAGGCAGGGAGC
CCATGCTCATGGTGAAGGTATGCTTCAGAAGTGTCTTCTGATGACTTCGTAAGTGCCCTGTTCCGACT
TGGATCTGGACTTCGAAACTTCTCATGGATTCTGAA **TAAAAGAAACACTCTACACCTCTAATCAAGGTATGT**
AGTAATGACTTGTATAAAATGCTACAGCTGTGAGAGCTTGTGATTGTTCTGTTGATGTTGTTGATGTTG
TGAAAAACTTAAACTGGTAGAACTTGGATAAAATAATTGTTTAATTAAAAAAAAAAAAAA

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FIGURE 28

MLCVGRLGGLGARAAALPPRAGRGSLEAGIRARRVSTSWSVGAAFNVKPQGSRLDLFGERARLFGVPELSAPE
GFHIAQEKLRTTELLVDRACSTPPGPQTVLIFDELSDSLRCVADLADFVKIAHPEPAFREAAEACRSIGTMVE
KLNTNVDLYQSLQKLLADKKLVDSDLPETRRVAELFMDFEISGIHLDKQKRKRAVDLNKILDLSSTFLMGTNF
PNKIEKHLLEHIRRNFTSAGDHIIIDGLHAESPDDLVREAAYKIFLYPNAGQLKCLEELLSSRDLLAKLGVYST
FSHRALQGTIAKNPETVMQFLEKLSDKLSERTLKDFEMIRGMKMKLNAQNSEVMPWDPPYSGVIRAERYNIEPS
LYCPFFSLGACMEGLNILLNRLLGISLYAEQPAKGEVWSEDVRKLAVVHESEGLLGYIYCFFFQRADKPHQDCHF
TIRGGRLKEDGDYQLPLVVLMLNLPRSSRSPTLTPGMMENLFHEMGHAMHSMLGRTRYQHVTGTRCPDFAEV
PSILMEYFANDYRVVNQFARHYQTGQPLPKNMVSRLCESKKVCAAADMQLQVFYATLDQIYHGKHPLRNSTTDIL
KETQEKFYGLPYVPNTAWQLRFSHLVGYGARYYSYLMRAVASMVWKECFLQDPFNRAAGERYRREMLAHGGGRE
PMLMVEGMLQKCPSVDDFVSALVSDLDFETFLMDSE

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FIGURE 29

TTTGCAAATAGTAACGACAAAGATGATCAAGTTAAATTGCCATTGGCAGTGAAGGTGCTATCCCCGGAAGAT
GGAAAAGCAGATATTGTGAGAGCCGCTCAGGACTTTGCCAGTTAGTAGCCCAGAACAGCAAAGGAGACCCAAAGAT
TTGGATGTAGATATGTTAGTTACTCAGTTCAAATGGTTGCCTGATCCTGATT**TAG**TACTGAAGTTCGGTCCTG
TGGACAGCACACGAGGCTTCTTACCTGGCACATCAGATTGACTGAGACTGTCTCTTGCTTCCCACATCAAACA
TCAGTTATGAGGACTTTCTGCCCTCGTCATTATGCAGCCTGTGAACAGCGCTGGGAAAGTCGTGGTCAT
TGGTTGCATAATTCCATTGAGCTATGGAGGAAGGACCAAGTGACTCTGATTTAGAAAGCACCTATGAAACC
CTGTACACACCTATGAAACCTGTACACACCTAGTTCATATACTTCATAATTATCAACAAACACAAAAAGTGT
CTTACTTGAGAGTGAGTGCGTGTGCGTGCACACATGTGCACGTTGTATGTGTTGAAATAAACATAAAAT
GGGGACGTGTTGGAGAAGGAAATACATAGACCTACAACTTGAGCATATAGCAGTGATGTTAGGAACGTGAAAT
GTCACACTTAATAAGTCTCAGCCCAGCTACTTCCCTGTTCTGTTGGGAGAAGAGGGCCTGATTAGAAACTGTT
CTGGTTGTGTTGGCGGGAGGGAAATAATTGTTCACTTCTTAGTGACCAAACCTTAATTAAAGAATA
ATATATTGACTTACTGAACTGAAGCATTCTGAGTGAAAGGAGCTCCAGAGGAAGAGGAGTTCTGTGTTGCTCACA
TGTTAAAGCTTGCTCACCTCAGAGCAGAGGAATACCTATCTACAGATATCCGCCATTTCATCTCTTCATT
ATAGTCAAACAGTGTGACTTGAGAGTGTG

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FIGURE 30

FANSNDKDDQVLNCHLAVKVLSPEDGKADIVRAAQDFCQLVAQKQRRPKDLDVVMLVYSVQMVLILI

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FIGURE 31

GAATTCTGCGGAGCCTGCGGGACGGCGGGTTGGCCGTAGGCAGCCGGACAGTGTGTACAGTGTGTTGGG
 CATGCACGTGATACTCACACAGTGGCTCTGCTCACCAACAGATGAAGACAGATGCACCAACGAGGGTCTGGAAT
 GGTCTGGAGTGGTCTGAAAGCAGGGTCAGATACCCCTGGAAAAGTGAAGCCGTGGAGCAATGATCTACAGG
 ACTGCTTCAAGGCTGATGGAACCAACCTGTAGAGGTCCATCTGCGTTAGACCCAGACGATGCCAGAGCTATGA
 CTGGGCCTGCAAGGTGTCGGCGAGGGAGATCAGCCATGGGAGCAGCACAGGAGGAAGGCCCTGAGGTCCGGGA
 AGAGGAGGAGAAAGAGGAAGTGGCAGAGGCAGAAGGAGCCCCAGAGCTCAATGGGGGACCAACAGCATGCACCTCC
 TTCCAGCAGCTACACAGACCTCTCCCGAGCTCTGCCACCCACTGCTGGACCAACTGCAGATGGGCTGTGA
 CGGGGCCTCATGCGGCAGCCTCAACATGGAGTGCAGGGTGTGCGGGGACAAGGCATGGGCTTCAACTACGGTGT
 TCATGCATGTGAGGGTGCAGGGCTTCTCCGTACGATCCGATGAAGCTGGAGTACGAGAAGTGTGAGCG
 CAGCTGCAAGATTCAAGAAGAACCGCAACAAGTGCAGTACTGCCGCTTCAAGAAGTGCCTGGCACTGGCAG
 GTCACACAAACGCTATCCGTTGGTGGATGCCGGAGGCTGAGAAGAGGAAGCTGGTGGCAGGGCTGACTGCAA
 CGAGGGGAGCCAGTACAACCCACAGGTGGCCGACCTGAAGGCCCTCTCCAAGCACATCTACAATGCCTACCTGAA
 AAACCTCAACATGACCAAAAGAAGGCCCGCAGCATTCTCACCGCAAAGCCAGCCACACGGGCCCTTGTGAT
 CCACGACATCGAGACATTGTGGCAGGCAGAGAAGGGCTGGTGTGAAAGCAGTTGGTGAATGGCCTGCCTCCCTA
 CAAGGAGATCAGCGTGCACGCTTCTACCGCTGCCAGTGCACACAGTGGAGACCGTGCAGGGACTACTGAGTT
 CGCCAAAGAGCATCCCCAGCTTCAGCAGCCTCTCAACGACCAGGTACCCCTCTCAAGTATGGCGTGCACGA
 GGCCATCTCGCCATGCTGGCTCTATCGTCAACAAGGACGGCTGCTGGTAGCCAACGGCAGTGGTTGTCAC
 CCGTGAGTCCCTGCGCAGCCTCCGCAAACCCCTCAAGTGTATCATTGAGCCTAAGTTGAATTGCTGTCAAGTT
 CAACGCCCTGGAACCTGATGACAGTGCACCTGGCCCTATTCAATTGCGGCCATATTCTGTGTGGAGACGGGCCAGG
 CCTCATGAACGTTCCACGGTGGAGGCTATCCAGGACACCCTCGTGCCTCGAATTCCACCTGCAGGCCAA
 CCACCCCTGATGCCAGTACCTCTCCCCAAGCTGCTGCAGAAGATGGCTGACCTGCGGCAACTGGTCACCGAGCA
 CGCCCAAGATGATGCGAGCGGATCAAGAAGACCGAAACCGAGACCTCGCTGCACCCCTGCTCAGGAGATCTACAA
 GGACATGTACTTAACGGGCAGCCACCCAGGCTCCCTGCAGACTCCAATGGGCCAGCACTGGAGGGGCCACCCACA
 TGACTTTCCATTGACCAGCTCTTCTGTCTTGTCTCCCTTCTCAGTTCTCTCCCTCTCCCTTGTGACCTCCCTTCTAATT
 CCTGTTGCTCTGTTCTCCTTCTGTAGGTTCTCTCCCTCTCCCTTGTGACCTCCCTTGTGACCTCCCTTCTC
 TCCTATCCCCACGCTGTCCTCTTCTATTCTGTGAGATGTTGTATTATTCACCAAGCAGCATAGAACAGG
 ACCTCTGCTTTGACACCTTCTCCCTGGAGGAGCAGAAGAGAGTGGGCCCTGCCCTGCCCCATATTGACACCTGC
 AGGCTTAGGTCTCACTCTGTCCTGCTTCAGAGCAAAGACTTGAGCCATCCAAGAACACTAAGCTCTC
 TGGGCCTGGGTCAGGGCTAAGCATGGCCTGGACTGACTGCAGCCCCCTATAGTCATGGGTCCTGCTG
 CAAAGGACAGTGGCAGACCCGGCAGTAGAGGCCAGATGCCCTCCCAAGACTGTCATTGCCCTCCGATCGTGAG
 GCCACCCACTGACCAATGATCCTCTCCAGCAGCACACCTCAGCCCCACTGACACCCAGTGTCTCCATCTCA
 CACTGGTTGCCAGGCCATGTTGCTGATGGCCCTCCAGCACACACACATAAGCACTGAAATCACTTACCTGC
 AGGCACCATGACACCTCCCTCCCTGAGGCAGGTGAGAACCCAGAGAGAGGGGCCAGGTGAGCAGGCAG
 GGCTGGGCCAGGTCTCGGGGAGGCAGGGCTCTGCAGGTCTGGTGGTCAGCCCAGCACCTGCCAGTGGGA
 GCTTCCCGGGATAAAACTGAGCCTGTTGATGTCATTGTCATTGTGCCCCAATAGCTACTGCCCTCCCCCTTCCC
 TTTACTCAGCCCAGCTGGCACCTAGAAGTCTCCCTGCACAGCCTCTAGTGTCCGGGACCTTGTGGACCAGTC
 CCACACCGCTGGCCCTGCCCTCCCCCTGCTCCAGGTTGAGGTGCGCTCACCTCAGAGCAGGCCAAAGCACAGC
 TGGGCATGCCATGTCAGAGGGCGCAGAGCCCTCAGGCCCTGAGGGCAAGGGCTGGCTGGAGTCTCAGAGCA
 CAGAGGTAGGAGAACTGGGGTCAAGCCCAGGCTCTGGGCTCTGCCCTGGTCTGGCCTCCCTCCAAGGAGCCATTCT
 ATGTGACTCTGGGTTGAAGTGCCTGACGCCAGCCCTGCCCTGACGGXXXXXXXXGATCACTCTGCTGGCAGGATTCTCC
 CGCTCCCCACCTACCCAGCTGATGGGGTGTGGGTCTTCTTCAGCCAAGGCTATGAAGGGACAGCTGCTGGGA
 CCCACCTCCCCCTCCCCGCCACATGCCGCTCCCTGCCCTGCCACCCGGGTCTGGTGTGAGGATAACAGCTCTT
 CTCAGTGTCTGAACAATCTCAAAATTGAAATGTATATTGCTAGGAGCCCCAGCTCCGTGTTTAAT
 AAATAGTGTACACAGACTGACGAAACTTAAATAATGGAAATTAAATATTAAAAAAAGCGGCCCGAATT
 C

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FIGURE 32

MEQPQEEAPEVREEEKEEVAEAEGAPELNGGPQHALPSSSYTDLSRSSSPPSILLDQLQMGCAGASCGLNMECR
VCGDKASGFHYGVHACEGCKGFFRRTIRMKLEYEKERSCKIQKKRNKCQYCRFQKCLALGMSHNAIRFGRMPE
AEKRKLVAGLTANEQSQYNPQVADLKAFSKHIYNAYLKNFMNTKKKARSILTGKASHTAPFVIHDIETLWQAEKG
LVWKQLVNGLPPYKEISVHVFYRCQCTTVETVRELTEFAKSIPSFSILFLNDQVTLLKYGVHEAIFAMLASIVNK
DGLLVANGSGFVTREFLRSLRKPFSDIEPKFEFAVKFNAAELDDSDLALFIAAIILCGDRPGLMNVPVREAIQD
TILRALEFHQLQANHPDAQYLFPKLLQKMAIDLQLVTEHAQMMQRRIKKTETETSLHPLLQEIYKDMY

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FIGURE 33A

GGACACGGAGCCGCGAGGAGACAGCTGAGGCCCGGGAGACCAGGGGTGAAGCCTGGAGACCCCTTGCCTGG
 CCTAGCTCAGGCCCGGGATGCTTGGCATGTCCCTGAGCCCCACAGAAGAGCAGCCAATGGCAGTGG
 AGCTGAGGAGACCCCAGGCTCCTGGACACGCTCTGCAAGACTCCCAGCCCTGCTGAACCCAGAGGACCTCT
 GCCATGGAAGGCCAGGGACGGTGCTCAGCCAGGAGGAGGTGGAGGGCGAGCTGGCTGAGCTGCCATGGCTT
 TCTGGCAGCAGGAAGGCCAGGCCACACTTGCTGCTGCTGGCCACGAAGCAGTTCACAGCTGCTACAGAC
 AGACCTTCCGAATTAGGAAGTTGCCAGGGAGGAAGAAGAAGAGGGAGGAGGACATGACGAGGAGGAAAGGC
 CCCTGTGACCTTGCTGGATGCCAAAGCCTGGCACAGAGTTCTTAAACGCCCTTGGGAAGTCGCCAGTG
 GCAGAACGAGGTGCCATTGGCTGCCGGCCTCACAGCGGAGTGGCTGGTCTCCATCCACGCCATCCGGAACAC
 TCGCCGAAGATGGAGGACGGCACGTGCTCCCTCCCTCAACCAGCTTCCGGCTGTGACCCCTGTGAA
 CCGCGCCTACTTGCTGTGTTGATGGTCACGGAGGCGTGGATGCTGCGAGGTACGCCGTGACGTGACAC
 CAACGCTGCCGCCAGCCAGAGCTGCCACAGACCCCTGAGGGAGCCCTCAGAGAACGCTCCGGCGACCGACCA
 GATGTTCTCAGGAAGCCAAGCGAGAGCGGCTGAGCGGCCACCACAGGTGTGTGCGCTCATTGAGGAGC
 GACCCCTGCACGTCGCCCTGGCTCGGGATTCCAGGTATTGGTACAGCAGGGACAGGTGGTAAGCTGATGGA
 GCCACACAGACCAGAACGGCAGGATGAGAAGGCGCATTGAAGCATTGGTGGCTTGTGTCACATGGACTG
 CTGGAGAGTCACGGGACCCCTGGCGTCCAGAGCCATGGGATGCTTCCAGAACGCCCTACGTGCTGGGGA
 GGCGGATGCACTCCCGGGCGTGAAGGGCTCCGAGGACTACCTGCTGCTGCTGTGATGGCTTCTTGACGT
 CGTACCCACCAGGAAGTTGGCTGGCCGGAGCGGGCTCCACGACAACATCACGGTATGGTGGCTTCCAGGG
 CCCCCAAGAGCTGCTGGAGGGCGGGAACCAAGGGAGAACGGGACCCCCAGGCAGAACGGAGGAGGAGGACTTG
 CTCCAGCCTTCCAGAACCTGAGACCCAGGCTCCACCAAGGTAGTGGTTCCAGGCCCTGCCCTCC
 CTCCCACCTTGTCTTCTCCCTCAGAACGCTCAGGACCCACAGGTGGCAGGCAGTGGACAGGGTGCCGCC
 CCACAGTGTCTTCCCCAGCACCCAGGCCAGTGGACACCCCCCGAGCCCTGGTGGCTGTGGAACGTG
 ACTGGGTGGCGGGCAGATGGTGAAGGAGCTTAGGAGACCTCACCAAAGAGAACGACGGGCTCTGCTCCC
 AGCTCCTATTAGGCCCGGGTGGGACAGAGGTCAAGGTGCCAACGGCAGCCAAACAAAGACACTGGTGTG
 ATGGGGCAGCATGGTGTGCACTGGGACCCCTGGGCGGACCCAGGAGCCAAACTCTGAAGCACCCCTGGG
 AGGCCAGCAGCGGAGTGGCAGCCCCAGTTCCATTGCTCTCTGCGGCCAGGGCAGGTGGTTCATATT
 TACAGATATGCCAGCCAGTCTGGTGGCCACACCAGTGTCCAAAGAGGAGAGCGCAGCAGGCCAGGGTCT
 GTTCTGTAGCAGCCACCCCCCTGCCCTCAGGGCAGCCATGATGTGCTTGGCCACCAGGGCTTCCGG
 TGCTCTTCCCTGAGCCCGAACGGCGACGCACATGTGCTTTGTGGTGTGTTGTTTTCCAGGGAGG
 TCTAATTCCGAAGCAGTATTCCAGGTTCTTGTGTTATCAGTCCAAGATGACCTGTTGTGTCATAATT
 TAAGCAGAGCTTAGCATTATTATTAGAAAACCTAAGTATTACTTTAAAGCTATTCAAGGA
 CCTTTTTGCACTATTATTGAATTATTCTAAATCAGGATTGAAACAGGAACCTTCCAGGTGGTGTAAATA
 AGCCATTCAAGTGCCTTACACAGCTTGAAGAAACTAGGACTGAGTGGCTGGATAGGCCATTGAGGTTTT
 AGAAAAGCAGGATTGTTAGGGAGGCATGATTGGTGGAGATCTTCTGGAAGAGTTTCCGCTCTTG
 TGATGCTGAACACCCCCAAGGTTCTCCCTCCCCCGCTGCCAGGTGACTGGCAGGAGCTGCACTGCCACGTA
 GTGTTGCCCTGGGCCGACAGCGGGCTGGGCATCCGGGTGACCTGGCCCATCTGCCGCATTCCACCCCC
 TTGGGCCCTGGCTGGATCCCAGGCAGAGGGACCTTGCTGCTGTGATTGGAACATTCCAAATCTTGTAATT
 TGTAATCAAATTGGTCTCATTGGAAAGACTCTTAATTAAAGAGGCTCAGGCAAGCACAGAGGCAGCCCGTGG
 TCTGCTCAGTCTGGAGGCAGGGATGCTGCTGGAGTCCATGGCACAGGCCACAGCCCTCACCTGCCGCG
 GTGGCTGGCAGCACGCCCTGCCCTGCTGCCCTGAACAGGCATGAGAGCCTCACGCTCCCTAGTGCAC
 CCTGAGAGGGGCTCACAAGTGACCGATCCTGGGTGCCCTCAGGGAGCTCACTGAGGGCGTCAAAGTTGAAAGTG
 GCAAGGCTGGGGAGGGTGTGGTAGAGGGAAGAGGGCAGGGGCTAGGGAGGACTCAGAGGCCATCTGCAGG
 GCCAACAGGAAGGGCTGAGCTGGAGGTGGGCAGGGCTGCTCCAGGCAGGTAGAGCAGTCAGGGAGGAGGA
 GAGGAGAAAGGGAGGAAGCTGGCTGTTGGTCCCCATGAAGGCATTAGAGTCCACCTGCAAGACAGCGAGAGC
 CCAGGAAGGTTGCACAGCTGCCCCAACGCACCTTGGCCTCCTCAGCTGCCAGGGAGCAGCTAGAGCCG
 CCTTCCCCGTGGGAGCCCTGTCCCACAGGGAGGGAGCCAGCTTGTGCTGGGCCCTACCTGCATGCCAGC
 CTTACCCCTCATTCTCACAGCACAGATGAGGTTGAGACCATGCACTGAGTCATTGCTTAAGGTCTTATTAC
 AAAAAAAACCTAAACATAGTCGCTGTCAATTAGACAATTAGAGAACATGGTGGCCACAAACAATGACCAAGTAT

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FIGURE 33B

TGCTTGGCTTAACCTGAAGGCCTGCTGTCCTCTGGGGTCAGGGACGCAGCTCCACCCTCACCCTAGCCCCA
CCCTGCCGTGGCATAACCTGACGAAGAGAGAGAATGATTGGCATCTGCTTTCTTTCTTGCTAATAAT
TCTGTTCTGGCTGCCAGAGTGAAGTTCACCATGTGGAGGTTGGCTCCTATCACCTGGTGGTCTGATTCTA
CCCTAGCCTGAGGCTCCACTGGAAGATCTGCAGCCTCAGTGTATGGAAACCCCTTCCCCAGGCTGTCCCAGC
ACTGCCGCTCCCCACCCCTGAGCCAGGACCCAGAGGATGGCATGCCATGCCCTGCTGCCAGAGGTCTGGTGCAG
CACTGGGAGCTGCTCCGCCCTGCCTGGGGCCGAGGGAGCCCTGTCACAGCAGCTGGCAGAGA
GGAGCGCTTCCATCTGACCAGGACTGCACCAAGAACGACCCAGGTGTCTCAGCCTCAACCTCCGGGGCAG
CTTCTCTCCAGCCACAGTCCCAGGGCCCTAGCCAGGGACACTGGTCTGTAAATTGTAATCCTTCTCCAG
CCCAGCTCTCCACTGTTCTGTGAGCTGAGCAGGCAGTCACCTCTGAGTGTCCCTTTGTAAGGCCAGG
GGTTGCACTGAGTCTGCAGAGGCCGACCTCTAGAACGCTGTGGGTGCAAGTGAGCCGGGTGCTCTGGGAG
ATGCTGCCAGCACACAGGGCCCTCTGCTGCCAGCAGGTGGGTGTTAAGTCTTATTAGTGTCTATTCTAA
AATTAAGTGGGCTGGAGAAGAATGGAGCTCCACATGCCAGCACGTATATGGAATACAAAAGCTGGGAAGCAGG
GCCTGCCCTACAGGTGTGGCTGACTCTGAGCCCAGGCCTGCAGGGTGGAGGGCAGTCCTCAGAACATCCCAGAGG
CAGTCCCAGCCTCAGAACCCAGGATAGGAATGGGTGTGTTAGTGGGAAAGGGACGGGGTGCAGACGGCAGGG
CCAGTATGGGCCCCCTCCTCTCCTCTCTATGGTAGGCCAGCGTGGCACCGGGCGTCTAGCCGT
GTTCCCAGGGCTGGAGGACAGCTCTGCCCTCTAGGCCCTAGCCTCTGCTCCAGCTAAATGTAAGCCAGTTGG
GCTGTGTTAAGGAAGCAGTGTGTTGGTTGATTCTGCCTCTGCTAGCTCAAGGGGGCAGCCCCCAGAGTCCTG
TGCATTCTGCCAAGGCTCCATAGCTTGCCTAGCAGGAGCTCTGCCATTCCGGTGCAGTGCAGGCCTGCGA
AGGGTTATCTGCCTCGTCCTGGCTCTGCATGGGAGTTGTGTTCTGTGCAAGGGGGAGCTTG
CAGGACAGGATGACTGCTTCCCTATTCTTAGGGACAAGTCCAAGATGCCAGAAAGGCAGTCTCCAAGGACCC
ACCATGCAGAAGTGTCAATAACCACAAGTTCTG

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FIGURE 34

MSSGAPOKSSPMASGAEETPGFLDTLLQDFPALLNPEDPLPWKAPGTVLSQEEVEGELAELAMGFLGSRKAPPPL
AAALAHEAVSQLLQTDLSEFRKLPREEEEEEEDEEEKAPVTLLDAQSLAQSFNFNLWEVAGQWQKQVPLAARA
SQRQWLVSIAIRNTRRKMEDRHVSLPSFNQLFGLSDPVNRAYFAVFDGHGGVDAARYAAVHVHTNAARQPELPT
DPEGALREAFRRTDQMFLRKAKRERLQSGTTGVCALIAGATLHVAWLGDSQVILVQQGQVVKLMEPHRPERQDEK
ARIEALGGFVSHMDCWRVNGTLAVSRAIGDVFQKPYVSGEADAASRALTGSEDYLLLACDGFFDVVPHQEVVGLV
QSHLTRQQGSGLRVAEELVAAARERGSHDNITVMVVFLRDPQELLEGGNQGE GDPQAEGRQRQDLPSSLPEPETQA
PPRS

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FIGURE 35

ATGGCGGGCGGCGTAGCGGCTCCACTCGCCGCCGGGGTGAGGAGGCAGCCACGACCTCCGTGCCGGGTCT
CCAGGTCTGCCGGGGAGACGCACTGCAGAGCGGGCCCTAGAGGACGCCACCGGACCCCTGAACCTGTCT
AACCGGCCCTGAAGCAGTCTCCCCGGGGCGCGGCCCTAGCTACGACCTGTCAAGACATCACCCAGGCTGACCTG
TCCCAGAACCGGTTCCCGAGGTGCCCGAGGCAGGCGGTGCCAGCTGGTGTCCCTGGAGGGCTGAGCCTTACAC
AATTGCCTGAGATGCCGAACCCAGCCTGGGAATCTCACAGCCCTCACCTACCTCAACCTCAGCCGAAACAG
CTGTCGCTGCTGCCACCCATCTGCCAGCTGCCCTGAGGGCTCTCATGTCAGCAACAAGCTGGGAGCC
CTGCCCTGACATCGGCACCCCTGGGAAGCCTGCGACAGCTGACGTGAGCAGCAACGAGCTCCAATCCCTGCC
TCGGAACGTGTGGCTCTCTCCCTGCCGGACCTCAATGTCGGAGGAACCAGCTCAGTACGCTGCCGAAGAG
CTGGGGGACCTCCCTGGTCCGCTGGATTCTCTGTAAACCGCTCTCCGAATCCAGTCTCCTCTGCC
CTGAGGCACCTGCAGGTCAATTCTGCTGGACAGCAACCCCTGCAAGACTCCACCTGCCAGGTCTGCCGAAGGG
AAACTCACATCTCAAGTATTGTCCACAGAGGCCGGCAGCGTGGGTGCCCTGGGGGACCTGCCCTTCT
CGGCCCCGAGTTCACTCCCTGCCCTGCAAGAGGATCTATTCCGGACATCGTACGATGGTGGGCTGGACTCA
GGCTTCCACAGCGTTGATAGTGGCAGCAAGAGGTGGTGGAAATGAGTCACAGATGAATTTCAGAGCTGTCA
TTCCGGATCTCAGAGCTGCCCGGGAGCCCGGGGGCCAGAGAACGCAAGGAGGATGGCTCAGCGGACGGAGAC
CCTGTGCAAGATTGACTTCATCGACAGCCATGTCGGGGAGGATGAAGAGCGAGGCACTGTGGAGGAGCAGCGA
CCACCCGAATTAAGCCCTGGGGCAGGGGACAGGGAGAGGGACCAACAGCAGGCCGGAGGAGCCGGCAGGGAG
GAGCGGGCGGCCGGACACCTGCACTGTGGCAGGAGCAGGAAACGCCGGCAGCAGCAGCAGAGCGGGCGTGG
GGGGCCCCGAGGAAGGATAGCCTCTGAAGCCAGGGCTCAGGGCTGTTGTGGAGGGCCGCCGTGTCCTACT
CAAGCCATGCACAACGGCTGCCCTAAGTCCAGTGCCTCCAAAGCAGGGGCTGCAGCGGGCAGGGAGCCCGCC
CCTGCCCTGCCCTCCAAAGAGCCCTTCCATAGCTGGACCAGCGACAGCACCTGCTCCACGCCACTTGGCTCC
ATTCAAGAGACAAACAGCTTCTCTCCGTTCTCTCTCAAGTGGCTCAGGCCCTTCTCACCAGACTCTGTC
CTGAGACCTCGGCGGTACCCCAAGGTTCCAGATGAGAAGGACTTAATGACTCAGCTGCCAGGTCTTGAGTCC
CGGCTGCAGCGGCCCTGCCTGAGGACCTGCCAGGCTCTGGCCAGTGGGTATCCTGTGCCAGCTGGCAAC
CAGCTACGGCCCGCCTCCGTGCCCTCATCCATGTGCCCTCCCTGCTGTGCCAAAACTCAGTGCCCTCAAGGCT
CGGAAGAATGTGGAGAGTTCTAGAAGCCTGTGCAAAATGGGGTGCCTGAGGCTGACCTGTGCTGCCCTCG
GATCTCTCCAGGGCACTGCCGGGGCTCGGACCGCGCTGGAGGCCGTGAAGCGGTGGGGGCAAGGCCCTA
CCGCCCTCTGGCCCCCTCTGGTCTGGCGCTCGTCGCTCTACGTGGCTCTCATGCTGCTGCTATGTC
ACCTACACTCGGCTCTGGATCCCCGTCCCCCAAGGTGGCTGGGAGGTGGCCCCCTGAGGATGACTCCACTA
GCCCTGGGACCCAAGTATGAAGCCAAAGCAGGACCTGCCAGGGACTGGATGGCTCTCATGCTGCTGCTATGTC
ACTGGCTGGGTGCTCAGGGAGCTGTGCGGTGGCTGAGGCTCCAGTGTCTGTCCCTCACCCTAGGGGCCA
ACTGTAGCTCAGGAGCCTCGTCTCAGGCCGGACGCTGTGTCACCCCTCATTCTGCCGCTGTATGAAGCAGCCT
CGGGCAGGGGTCTCAGGCCCGTGGCCCTGCCACAGGGCACTGGAATGGACAGCAGGCCAGATGCAGGGT
TCCCAGGGTGTGCTGTGAAGATGTCTCTCGGACCCCTGCTGCCCGGGCAGCGTGTGCTCTGTAC
TGTCCAAGGCCCCCAGCAGATGATGGCTCCCTGAAACTGCTGCCGCCCTCATGCTGCTGCCAGGGTGC
TCCCCGCCCATCACCTCCCCGGGGCCCTCCACTGCCAGGGCTGAGCTGACCTCTCTCACAGACCCAGACACCAC
TGCTGCAGATGAGCCAGGGGAGCCTAGGCCAGCTCTCCGCGTTGGCCCCCAGACCATACCTGTACCCAC
CCAGCCCCCTGTGGTAGCCCCCAGCAGTTCTCAGGGTGTGACCTCTCTCCACAGACCCAGACACCATTGTC
CATAGCCTCTCAGGGCAGAGTGGCTGGTTGTGACAATAAACAGTGTGGTTGCA

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FIGURE 36

MAAAVAAPLAAGGEEAAATTSPGSPGLPGRRSAERALEDAVATGTLNLSNRRLKHFPRGAARSYDLSITQADL
SRNRFPEVPEAACQLVSLEGLSLYHNCLRCLNPALGNLTALTYLNLSRNQLSLLPPYICQLELRVLIVSNNKLGA
LPPDIGTLGSLRQLDVSSNELQSLPSELCGLSSLRDLNVRRNQLSTLPEELGDLPLVRLDFSCNRVSRIPVSFCR
LRHLQVILLDSNPLQSPPAQVCLKGKLHIFKYLSTEAGQRGSALGDLAPSRRPSFSPCPAEDLFPGHRYDGGLDS
GFHSVDSSGSKRWSGNESTDEFSELSFRISELAREPRGPRERKEDGSADGDPVQIDFIDSHVPGEDERGTVEEQR
PPELSPGAGDRERAPNSRREEPAGEERRRPDTLQLWQERERRQQQSGAWGAPRKDSLLKPGGLRAVVGAAAVST
QAMHNGSPKSSASQAGGCSGAGSPAPAPASQEPLPIAGPATAPAPRPLGSIQRPNSFLFRSSSQSGSGPSSPDSV
LRP RRYPQVDEKDLMTQLRQVLESRLQRPLPEDLAELASGVILCQLANQLRPRSVFIHVPSPAVPKLSALKA
RKNVESFILEACRKMGVPEADLCSPSDLLQGTARGLRTALEAVKRVGGKALPPLWPPSGLGGFVVFYVVLMLLYV
TYTRLLDPRSPQVAWEVAPSRTPLAPWDPKYEAKAGPRPVVSWGQTCGTGWGAQGAVRWEAPVLCPPHPRGP
TVAQEPRSQAGRCVTPHSGRCMKQPRAGVSGPWPLPQGTGMDSSRRPQMGSRWCAVKMSSRTLCCPGGSVFPC
CPRPPSR

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FIGURE 37

GC CGGGCC **ATGT** CCTCC CGCC CGCT CGCC ACCCC CGGGCC CGAGGATGAAGAAGGAC GAGTC GTT CCTG
GGCAAGCTGGCGGCACCCCTGGCCAGGAAGCGGAGGGCGCGAGGTGAGTGACCTGCAGGAAGAAGGCAAGAAT
GCCATCAACTCACCGATGTCCCCGCCCCCTGGTGGATGTTCACCCCTGAAGACACCCAGCTTGAGGAGAACGAGGAG
CGCACGATGATTGACCCCACCCAAGGAAGACCCCAAGTTCAAGGAACGGTCAAGGTCTCCTCGACTGGATT
AATGACGTGCTGGTGGAGGAGAGGATCATTGTGAAGCAGCTGGAGGAAGACCTGTATGACGCCAGGTGCTGCAG
AAGCTTGGAAAAACTGGCAGGGTCAAGCTGAATGTGGCTGAGGTGACACAGTCCGAAATAGGGCAGAACAG
AAGCTGCAAGCAGGTGCTGGAAAGCAGTACATGACCTGCTGCCCGAGGCTGGCGCTCCGGTGGACCGTGGAC
TCAATTACGGGAAGAACCTGGTGGCCATCTCACCTGCTGGTCTCTGGCCATGCACTCAGGGCCCCCATC
CGCCTTCTGAGCATGTAACGGTGCAGGTGGTGTGCAGGAAACGGGAAGGCCGTGCAATTCCAGCCACATC
TCGGAGGAGCTGACCACAACTACAGAGATGATGATGGCCGGTTCGAGCAGGATGCCCTGACACGCTGTCGAC
CACGCCCGGATAAGCTCAGCGTGGTGAAGAACGTTCTCATCACTTTGTGAACAAGCACCTGAACAAGCTGAAT
TTGGAGGTGACGGAACGGAGACCCAGTTGCAGATGGCGTGTACCTGGTCTGCTCATGGCCTCTGGAGAC
TACTTTGTTCTCACCACCTCTACCTGACTCCGGAAAGCTTCGATCAGAACGGTCCACAATGTGTCCTCGCC
TTTGAGCTGATGCTGGACGGAGGCCTCAAGAACCCAAGGCTGCTGAAAGACGGTTAACTTGGACCTCAA
TCCACCCCTGAGGGTTCTTACAACCTGTTACCAAGTACAAGAACGTGGAG **TGAC** GGGGGAGCTGTGGATGGTGG
CAGGAGTGTCCCAGCAAGAACGGCGGATCCGTCTGTGCCCTGTGCCCTTCCAGGGAGCCAGGCGCCATGGCTT
CTGGTCCAAGCTGTGTTGACTGTCATCCCCACCCCTACCTCACGCCCTGCCACCCCTGCCCTTTGG
TTGTTGTTCTTAATCTCCTCCATGTAAGTCCCAGTGGCAAGAGCCTTGAAGAACATGCAGGATTCTAACACTC
GTGCTTGCCTTGAAGCCTCGCGTCACTCAGTCGCGTGGGATGATGAGTCGTTGTCGCTTGGCGAAAG
ATGAAAAAAAGCCTGAACCCCAACCCCCAGCTGGTGAAGAGCACCCTGCATTCTGCTCATGGTCAGTTAGCGA
TCACAGGCCTTCAGAAGTACAACATCAGCTCAGCAGGAACGCCGGCTCCCGAGGGACCCAGGCTTGACGATTAC
CGGGGATCTCCTGGCTGGCTCTGGAAAGTGAGGCCTTTATTAAAAAATAAAAGGGTTTGCAGTTGAAA
AAAAAAAAAAAAAAAAAAAAA

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FIGURE 38

MSSAPRSPTPRPRRMKKDESFLGKLGGTLARKRRAREVSDLQEEGKNAINSPMSPALVDVHPEDTQLEENEERTM
IDPTSKEDPKFKELVKVLLDWINDVLVEERIIVKQLEEDLYDGQVLQKLLKLAGCKLNVAEVTOSEIGQKQKLO
TVLEAVHDLLRPRGWLRSVDSIHGKNLVAILHLLVSLAMHFRAPIRLPEHVTQVVVVRKREGLLHSSHISEE
LTTETEMMMGRFERDAFDTLFDHAPDKLSVVKSLITFVNKHNLKNLEVTELETQFADGVYLVLLMGILEDYFV
PLHHFYLTPEFDQKVHNVSFAFELMLDGGKKPKARPEDVNVNLKSTLRVLYNLFTKYKNVE

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FIGURE 39

GCTACGCGGGCCACGCTGCTGGCTGGCCTGACCTAGGCGCGGGTGGGCGGGCGCGCGGGCGGGCTGAGTGA
GCAAGACAAGACACTCAAGAAGAGCGAGCTGCGCCTGGTCCCAGGCTTGACGCAGAGCGGGCGAGA
CGGTGCCCGGCGGAATCTCTGAGCTCCGCCAGCTCTGGTGCAGCGCCAGTGGCCGCTTCGAAAGT
GAUTGGTGCCTGCCGCCTCTCGGTGCGGGACCATGAAGCTGCTGCCGTGGTGTGAAGCTTTCTG
GCTGCAGTTCTCTCGGCACTGGTGAUTGGCAGAGCCTGGAGAGCCTGGAGAGGGCTAGCTGCTGGAACCAGC
AACCCGGACCCCTCCACTGTATCCACGGAACAGCTGCTACCCCTAGGAGGCGGCCGGACGGAAAGTCCGTGAC
TTGCAAGAGGCAGATCTGGACCTTTGAGAGTCACCTTATCCTCCAAGCCACAAGCACTGGCCACACCAAACAAG
GAGGAGCACGGGAAAAGAAAGAAGAAAGGGCTAGGGAAGAAGAGGGACCCATGTCTCGGAAATACAAG
GACTTCTGCATCCATGGAGAATGCAAATATGTGAAGGAGCTCCGGCTCCCTCTGCATCTGCCACCCGGTTAC
CATGGAGAGAGGTGTCAUTGGCTGAGCCTCCAGTGGAAATCGCTTATATACCTATGACCACACAACCCTG
GCCGTGGTGGCTGTGGTGTCAUTCTGTCTGCTGGTCAUTGTGGGCTTCTCATGTTAGGTACCATAGG
AGAGGAGGTTATGATGTGGAAAATGAAGAGAAAGTGAAGTGGGATGACTAATCCCATGAAGAGACTTGTG
CTCAAGGAATCGGTGGGACTGCTACCTCTGAGAAGACACAAGGTGATTTCAGACTGCAGAGGGAAAGACTTC
CATCTAGTCACAAAGACTCCTCGTCCCAGTTGCCGTCTAGGATTGGGCTCCATAATTGCTTGCACAAATA
CCAGAGCCTTCAAGTGCCAACAGAGTATGCCATGGTATCTGGTAAGAAGAAAGCAAGGGACCTTC
ATGCCCTCTGATTCCCCTCCACCAACCCCCACTCCCTCATAAGTTGTTAAACACTTATCTCTGGATTAG
AATGCCGTTAAATTCCATATGCTCCAGGATCTTGACTGAAAAAAAAGAAGAAGAAGAAGGGAGAGCAAGAA
GGAAAGATTGTGAACTGGAAGAAAGCAACAAAGATTGAGAAGCCATGTACTCAAGTACCAAGGGATCTGCC
ATTGGGACCCCTCAGTGTGATTGAGTTAATGTGAAATACCAACAGCCTGAGAACTGAATTGGGACT
TCTACCCAGATGGAAAATAACAACATTTGTGTTGTTGTAATGCCCTTAAATTATATTTATT
TATTCTATGTATGTTAATTATTTAGTTAACATCTAACATAATTCAAGTGCCTAGACTGTACTTTG
GCAATTCTGGCCCTCCACTCCTCATCCCCACAATCTGGCTTAGTGCCACCCACCTTGCACAAAGCTAGGAT
GGTTCTGTGACCCATCTGTAGTAATTATTGTCTGTACATTCTGCAGATCTCCGTGGTCAGAGTGCCTACTG
CGGGAGCTCTGTATGGTCAGGATGTAGGGGTTAACCTGGTCAGAGCCACTCTAGAGTTGGACTTCAGTCTGCC
TAGGCGATTGTCTACCATTTGTGTTGAAAGCCAAGGTGCTGATGTCAAAGTGTAAACAGATATCAGTGTCT
CCCCGTGTCTCTCCCTGCCAAGTCTCAGAAGAGGTGGGCTCCATGCCTGTAGCTTCTGGTCCCTCACCCCC
CATGGCCCCAGGCCACAGCGTGGAACTCACTTCCCTGTGTCAAGACATTCTCTAACCTGCCATTCTCT
GGTGCTACTCCATGCAGGGTCAGTGCAGCAGAGGACAGTCTGGAGAAGGTATTAGCAAAGCAAAAGGCTGAGAA
GGAACAGGGAACATTGGAGCTGACTGTCTGGTAUTGATTACCTGCCAATTGCTACCGAGAAGGTTGGAGGTG
GGGAAGGCTTGTATAATCCACCCACCTCACCAAAACGATGAAGGTATGCTGTCAUTGGTCTTCTGGAAGTT
CTGGTGCCATTCTGAACTGTTACAACCTGTATTCCAAACCTGGTCAUTTATACCTTGAATCCAAATAAA
GATAACCCATTCCATAAAAAAAAAAAAAAA

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FIGURE 40

MKLLPSVVLKLFLAAVLSALVTGESLERLRRGLAAGTSNPDPPTVSTDQLLPLGGGRDRKVRDLQEADLDLLRVT
LSSKPQALATPNKEEHGKRKKKGKGLGKRDPCLRKYKDFCIHGECKYVKELRAPSCICHPGYHGERCHGLSLPV
ENRLYTYDHTTILAVVAVVLSVCLLVIVGLLMFRYHRRGGYDVENEEKVKLGMTNSH

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FIGURE 41

ACCGCGTCCGCTTCGGAATGAGAGACTCAACCATAATAGAAAGAATGGAGAACTATTAACCACCATTCTTCAGTGG
GCTGTGATTTCAGAGGGAAACTAAGAAATGGTTTCCATACTGGAACCCAAAGTAAAGACACTCAAGGACA
GACATTTGGCAGAGCATAG**TGAA**ATGGCAAGTCCCTGGCTTCCTCTGCTCAACTTCATGTCCTCCCTC
TTCTGGTCCAGCTGCTACCTGCTCAGCTCAGTTCTGTGCTTGGACCCTCTGGGCCATCCTGGCCATG
GTGGGTGAAGACGCTGATCGCCCTGTACCTGTCAGCTCAGGGACCATGGAGCTGAGGTGGGTG
AGTCCAGCCTAAGGCAGGTGGTGAACGTGATGCAGATGGAAGGAAAGTGGAAAGACAGGCAGAGTCACCATAT
CGAGGGAGAACTTCGATTCTGGGGATGGCATCACTGCAGGGAAAGGCTCTCCGAATACACAACGTACAGCC
TCTGACAGTGGAAAGTACTTGTGTTATTCCAAGATGGTACTTCTACGAAAAGCCCTGGTGGAGCTGAAGGTT
GCAGCATTGGTTCTGATCTCACATTGAAGTGAAGGTTATGAGGATGGAGGGATCCATCTGGAGTGCAGGTCC
ACTGGCTGGTACCCCCAACCCAAATAAGTGGAGCAGACCCAAGGGAGAGAACATCCGGCTGTGGAAGCACCT
GTGGTGCAGATGGAGTGGCCTGTATGCAGTAGCAGCATCTGTGATCATGAGAGGCAGCTCTGGTGGGGTGT
TCCTGCATCATCAGAAATTCCCTCCTCGGCCTGGAAAAGACAGCCAGCATA**TCC**ATCGCAGACCCCTTCTCAGG
AGCGCCCAGCCCTGGATCGCCGCTGGCAGGGACCCCTGCCTATCTGTTGCTGCTCTCGCAGGAGCCAGTTAC
TTCTTGTGGAGACAACAGAAGGAAAAATTGCTCTGTCCAGGGAGACAGAAAGAGAGCAGAGATGAAAGAAATG
GGATACGCTGCAACAGAGCAAGAAATAAGCTAAGAGAGAAAGCTCCAGGAGGAACACTCAAGTGGAGGAAATCCAG
TACATGGCTCGTGGAGAGAAGTCTTGGCCTATCATGAATGGAAAATGGCCCTCTCAAACCTGCGGATGTGATT
CTGGATCCAGACACGGCAAACGCCATCCTCTTGTGAGGACCAGAGGAGTGTGCAGCGTGTGAAGAGCCG
CGGGATCTGCCAGACAACCCCTGAGAGATTGAAATGGCCTACTGTGTCCTGGCTGTGAAAACACTCACATCAGGG
AGACATTACTGGGAGGTGGAAGTGGGGGACAGAAAAGAGTGGCATATTGGGTATGTAGTAAGAACGTGGAGAGG
AAAAAAGGTTGGTCAAATGACACCGAGAACGGATACTGGACTATGGCCTGACTGATGGAATAAGTATCGG
GCTCTCACTGAGCCCAGAACCAACCTGAAACTTCTGAGCCTCTAGGAAAGTGGGATCTCCTGGACTATGAG
ACTGGAGAGATCTGTTCTATAATGCCACAGATGGATCTCATATCTACACCTTCCGACGCCCTTTCTGAG
CCTCTATATCCTTTTCAAAATTGACCTTGGAGGCCACTGCCCTGACCATTGCCAATACCAAAGAAGTA
GAGAGTCCCCGATCCTGACCTAGTGCCTGATCATTCCCTGGAGACACCACTGACCCGGCTTAGCTAATGAA
AGTGGGAGCCTCAGGCTGAAGTAACATCTGCTTCTCCCTGCCACCCCTGGAGCTGAGGTCTCCCTCTGCA
ACAACCAATCAGAACATAAGCTACAGGCACGCACTGAAGCACTTACT**TGAT**ATTCAATTCCATTATTCCATATGA
CAGTTGTTGAGTTCGTACCAACCTTATTGCCCCCTATACAGATAAGGAAACTGGGTGAGAAAGGTGAATT
AACTTACAAAGTAGACATGACAAGTGAACAGCAGAGCTGGGATCTAACAGCAATAACTAACATTAACAGAGAA
TTAAAAATGTTCTAGTGTGTTATAAGCTTGGGATGTCACTCCTTAATCCTCACACACCCCTGTCGGG
TAGTCATATTGCAAGTATGGAAGCTGAGGCAGGGCAACATGAAGTAACCTACATAATTCAAGTAATTGTT
GCAGTTGGGAGATGTTCAGCCTTAGTCCCTGGCTAATTGCCCTGTTCTTCCAGCCTGATTGTTTCCCACAGG
AAGAGCCCACATGTAGCCCTGAGGTTCTCCAGGACAGCTGCAGGGTAGAGATCATTTAAGTGTGTTGG
GTTGACATCCCTATTGACTCTTCCCAGCTGATATCAGAGACTAGACCCAGCACTCCTGATTAGCTCTGAG
AGTGTCTGGTTGAGAGATAACCTCATAGTACCAACATGACATGTGACTTGGAAAGAGACTAGAGGCCACACTT
GATAAAATCATGGGCACAGATATGTCACCCACCCAAACAAATGTGATAAGTGTGAGCCAGGCCAGCCTTCC
TTCAATCAAGGTTCCAGGCAGAGCAAATACCCACTAGAGATTCTCTGTGATATAGGAAATTGGATCAAGGAAGCT
AAAAGAATTACAGGGATGTTAAACCCATATTCCCTTCAACTGCTGCCCTGCTAGGGAAAACGTCTCCTCATTATCATCACTATT
ATTGCTCACCACTGTATCCCCCTACTTGGCAAGTGGTTGTCAGTTCAAGTTCAATAATGTGTTAATAAT
GAAAAA

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FIGURE 42

MKMASSLAFLNNFHVSFLVQLLTPCSAQFSVLGPSPITLAMVGEDADLPCHLFPTMSAETMELRWVSSSLRQV
VNJVADGKEVEDRQSAPYRGRTSILRDGITAGKAALRIHNTASDSGKYL CYFQDGDFYEKALVELKVAALGSDL
HIEVKGYEDGGIHLECRSTGWPQPQIKWSDTKGENIPAVEAPVVADGVGLYAVAASVIMRGSSGGVSCIIRNS
LLGLEKTASISIADPFFRSAQWPWIAALAGTLPISSLLAGASYFLWRQQKEKIALSRETEREREMKEMGYAATEQ
EISLREKLQEELKWRKIQYMRAGEKSLAYHEWKMALFKPADVILDPTANAILLVSEDQRSVQRAEPRDLPDNP
ERFEWRYCVLGCENFSGRHYWEVEVGRKEWHIGVCSKNVERKKGWVKMTPENGYWTMGLTDGNKYRALTEPRT
NLKLPEPPRKVGIFLDYETGEISFYNATDGSHIYTFPHASFSEPLYPVFRILTLLEPTALTICPIPKEVESSPD
LVPDHSLETPLTPGLANESGEPQAEVTSLLLPAHGAEVSPSATTNQNHKLQARTEALY

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FIGURE 43

GGCACGAGGGTAGTGAGCGGTTTCAAGGATGTGAGGGCCCGCAGGAGCCGAGTCAGGCTCTCTCCACTGCCTGC
CCGCCACCGTCAAGCTCTGGCCGGCGTCCCCACAGTCCCCATGGTGGCAGCCCCCGCGCGGGACCCCTGA
TCGGCAGCGGCATGCCAGGGAGCCCAAGCACCTGGCGTCCCACAGGGCGAGGGCCGAGCTCTCAGCATCCACAGCCTCC
GAGAGCTGAGCAGCACGACGGGGCCCCAGGGCCAGGGCGAGGGCCGAGCTCTCAGCATCCACAGCCTCC
CCAGTGGTCCCAGCAGCCCCCTCCCAACCGAGGAGCAGCCTGTGGCCAGCTGGCCCTGTCTCGAGCGGCTGT
TGCAGGACCCGCTGGGCTGGCTTACTCACTGAGTTCTGAAGAAGGAGTTCAGCGCGAAAACGTGACTTTCT
GGAAGGCCTGCGAGCGCTTCCAGCAGATCCCAGCAGCGATAACCCAGCAGCTAGCTCAGGAGGCCGCAACATCT
ACCAGGAGTTCTGTCCAGCCAGGGCTGAGCCCAGTGAACATCGACCGTCAGGCCCTGGCTTGGCGAGGAGGTG
TGGCGAGCCCCGGCGGACATGTTGGGCACAGCAGCTCAGATCTCAACTTGATGAAGTTGACAGCTATG
CGCGCTTCGTCAAGTCCCCTGTACCGCAGTGCCTGCTAGCCGAAGCCGAGGGACGCCCTTGCGGGAACCTG
GCTCCTCGCGCTCGGAGCCCTGACGCCAGAGAAGAAGCCGAAGCTGAAGCCGGGAAGTCGCTGCCGTGG
GTGTGGAGGAGTTGGGCAGCTGCCACCCGTTAGGGTCTGGGGCCGCCCTCCGCAAGTCCTCCGCCGGG
AGCTGGCGGGACTGCAAACGCCGCTTGCGCCGAGAGTCTCAGGGCTCCCTCAACTCCTCCGCCAGCCTGGACC
TTGGCTTCCTAGCCTCGTCAGCAGCAAATCTGAGAGCCACCGGAAGAGCCTTGGGAGCACGGAGGGTAAAGTG
AAAGCCGCCAGGGAAAGTACTGCTGTGTACCTGCCGATGGCACAGCCTCTGGCCAGACCTGGCC
TCACCATCCGAGACATGCTGGCAGGGATCTGTGAGAAACGAGGCCCTCTCACCTGACATCAAGGTCTACCTGG
TGGGCAATGAACAGGCCCTGGCCTGGATCAGGACTGACCGTGTGGCGGATCAGGAAGTGCCTGGCTGGAAAACA
GGATCACCTCGAGCTGGAGCTGACGGCGCTGGAGCGCGTGGTACGAATCTCAGCCAAGGCCACCAAGCGGCTGC
AGGAGGCCCTGACGCCATTCTGGAGAAGCACGGCTGAGGCCGCTAGAGGTGGCTGCACCGGCCAGGCCAGA
AACAGCCTCTGGATCTGGGAAGCTAGTGAGCTGGTGGCGGCCAGAGACTGGTTTGGACACTCTTCAGGTG
TGAAGATCTCAAAGCCCGTACAATCTCCCTGCCGACGCCAGGGCTGCCACCTAGAACTCAGGATAAGGCCA
CCCATCCCCCTCCAGCGTCCCCCAGTTCTCTGGTGAAGGTGCCAGTAGTGCACGCCAGGGCTTCTGAGG
ACATCGAAGGCCCTGGTGGAGCTGCTGAACCGGGTGCAGAGCAGCGGGGCCAGCACCAGAGGGGCCCTCTGAGGA
AAGAGGACCTGGTACTTCCAGAATTCTGCAGCTGCCGCCAAGGGGCCAGCTCGAGGAGACCCACACAGA
CCAAATCAGCAGGCCAGCCCATGGGGGATCCTGAACTCCACCAACGACTGCCCTTGACAGCTACCCAACA
GTCCAGGACAGCTGCATGGCACCGGGGGCGAGCATGCCATGGTCCGCTCTGCATGCCCTGTCTGCCATG
AGTGTCCCTGGCCCTTCTGCATGGCAGGCCCGCAGGAAGAGCCGGTAGGGTGGAAAGGGGACTCAGATGA
GACACACCCCACAGCTGCCACCGCCTGTCCCTCAACAAGCTCACCCCCAATCCCTGCAGCCAGGCCACAATGG
GGGAGGTGAGTCCAGCCCTTGGAACAGGCTTGCACATGGAGGGATGGCGTTGGCAGTGCCAGCCTCCCCAG
CCTGTGCCAAGCTCAACAGGGCAAGAGGAGGGGCCGCCCTCAGGAAGCTGGTATGAGTAAGGCCCTGA
GGGTGCAGGCAGGCAGGCCCTGTACCCCACCCACATAGACTATACTGTACATACAGATTTGCAGTAGGCTGGGG
CAGCTGGTTTGTCTTGATGTACTGTTATTATAATTATTCTGCAAAAAAAAAAAAAAA
AA

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FIGURE 44

MPGKP KHLGVPNGRMVLA VSDGELSSTTGPQGQGEGRGSSLSIHSLPSGPSSPFPTEEQPV ASWALSFERLLQDP
LGLAYFT EFLKKEFSAENVT FWKACERFQQIPASDTQQLAQEARNIYQEF LSSQALSPVNIDRQAWLGEEVLAEP
RPDMFRAQQLQIFNLMKFD SYARFVKSPLYRECLLAEAEGRPLREP GSSRLGSPDATRKKPKLPGKSLPLGVEE
LGQLPPVEGPGGRPLRKSFRRELGGTANAALRRESQGSLNSSASLDLGFLAFVSSKSESHRKSLGSTEGESESRP
GKYCCVYLPDGTASLALARPLTIRDMLAGICEKRLSLPDIKVYLVGNEQALVLDQDCTVLADQEVRL ENRITF
ELELTALERVVRI SAKPTKRLQEALQP ILEKHGLSPLEVVLHRPGEKQPLDLGKLVSSVAAQRLVLDLPGVKIS
KARDKSPCRSQGCPPRTQDKATHPPPASPSSLVKVPSSATGKRQTCDIEGLVELLN RVQSSGAHDQRGLLRKEDL
VLPEFLQLPAQGPSEETPPQTKSAAQPIGGSLNSTTDSAL

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FIGURE 45

CCCCCTGGCCGCCGACAGCGCCGCCCTGCCCGCCATGGGTCGACAGAAGGAGCTGGTGTCCCCTGCGGGGA
GATGCTCCACATCCGCTACCGGCTGCTCCGACAGGCCTGCCGAGTGCCTGGGGACCCCTATCCTGGTGTATGTT
TGGCTGTGGCTCCGTGGCCCAGGTTGTGCTCAGCCGGGGCACCCACGGTGGTTCCCTCACCATCAACCTGGCCTT
TGGCTTGCTGTCACTCTGGCATCCTCATCGCTGGCCAGGTCTCTGGGGCCACCTGAACCTGCCGTGACCTT
TGCCATGTGCTTCTGGCTCGTGAGCCCTGGATCAAGCTGCCATCTACACCCCTGGCACAGACGCTGGAGCCTT
CTTGGGTGCTGGAATAGTTTGGGCTGTATTATGATGCAATCTGGCACTTCGCCGACAACCAGCTTTGTTTC
GGGCCCCAATGGCACAGCCGCATCTTGCTACCTACCCCTCTGGACACTGGATATGATCAATGGCTTCTTGA
CCAGTTCATAGGCACAGCCTCCCTATCGTGTGTGCTGCCATTGTTGACCCCTACAACAACCCCGTCCCCCG
AGGCCTGGAGGCCTTCACCGTGGGCTGGTGGTCTGGTATTGGCACCTCCATGGCTCAACTCCGGCTATG
CGTCAACCCCTGCCCGGACTTGGCCCCCGCTTTACAGCCCTGGGGCTGGGCTCTGCAGTCTCACGAC
CGGCCAGCATTGGTGGTGGGTGCCCATCGTGTCCCCACTCTGGCTCCATTGGGGTGTCTCGTGTACCAAGCT
GATGATGGCTGCCACCTGGAGCAGCCCCCACCTCCAACGGAGAAGAGAATGTGAAGCTGGCCATGTGAAGCA
CAAGGAGCAGATTGAGTGGCAGGGGCATCTCCCCACTCCGCTGCCCTGGCCTTGAGCATTCACTGACTGTCC
AAGGGCAGCTCCAAAGAGCCCCCTCACGATCACCCTTCAGGCTAAGGAGCTCCCTATCTACCCCTACCCCA
CGAGACAGCCCCCTCAGGATTCCACTGGACCTGCCAAATAGCACCTTAGGCCACTGCCCTAAGCTGGGGT
GAACCGGAATTGGGTCAATACATCCTTGTCTCCAAAGGAAGAGAATGGCAGCAGGTATGTGTGTG
ATGTGTGTGCATGTGTGCATGTGTGCAGGGGTGTGTGTGGGGGGTCCCAAGATATTCAAGGGCAAG
GGACCACTCGGAAGGGATTCTGGCTATTGGGGAGCCAGAGACAGGGGAAGGCAGCCTGCCATCTGTGCATAA
GGAGAGGAAAGTCCAGGGTGTGTATGTTCAGGGCTTACATGGAGGAGCTGCAGATAGATATGTGTTCTGT
GTATGTGTATGTCGCTTTCTAAGTGGGGCTTACAGGCTTTGGGAAGTAGGGTGGATGTGGTAGG
GCTGGGAGGAGGGGCCACAGCTAGGTTGGAGCTGGATGTACATAACATAAGTAGGAGCAGTGGACGTGTT
TCTGTACATAATGCAGGCATGAAGGGTGGAGTGAAGTCAGGTACATAAGTTCATGTTGCTTGTGTTGT
TTTAATGTATGTAGCAGATGTTACAGTCTAGGGATCCGGGATGGAGACCCCACTTAGAAAGGGTCGTCACT
CCTTAATCCTACTCAACAATGTACTCTTACTTTATATTAAAAAAATAAATATGTGCCAAAAAA
AAAAAAAAAA

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FIGURE 46

MGRQKELVSRGEMLHIRYRLLRQALAECLGTLILVMFGCGSVAQVVLSRGTHGGFLTINLAFGFAVTLGILIAQ
QVSGAHLNPAVTFAMCFLAREPWIKLPIYTLAQTLGAFLGAGIVFGLYYDAIWHFADNQLFVSGPNTAGIFATY
PSGHLDMINGFFDQFIGTASLIVCVLAIVDPYNNPVRGLEAFTVGLVVLVIGTSMGFNSGYAVNPARDFGPRLF
TALAGWGSAVFTTGQHWWWWPIVSPLLGSIAGVFVYQLMIGCHLEQPPPSNEEENVKLAHVKHKEQI

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FIGURE 47

TTTAGGTAAAACCGGATTAACCTGGGAAAAAAAAAGGAGAGAGAAGACAGTTCCCTTCCTGTAGAA
 ATTAACACAAATACAAATTGAGGAAGCTCTGCTACCCAGGCTGTCACTGGTAGAGAACTTGAAAGAACCTGTT
 GGATGGACACCTGGTTCAAAAGTCAGGTGTGGAGACTGTTAAATGGGAGGGCCTCATCCATAAATGATTCTGG
 CAACGTCTCTTCAGGTGGAGCTTGACGTCTTTAATGTTACTTGGGGAGGGAGTGCTCATTAAGGGATGCCAG
 GGCCAGCTCTGGGGTCTGGGGAGGCTGCGTCTCCCTGCTCTGCATGTCAAGGGCAGCAGGAAGGTT
 CCCTGCACCTGTCTGTCTGGCTCCCTGGTAGCCCCACTGTTCTGTGCTTCAGCACAGCCTGGTTGTCA
 AGAGGCACATAGTGGGGCTGGGCTGCATGGCACAGGGCTATGTCGCTGCTGGTTATTTAATTTCAGCCTTA
 AGTTTCTTAATATTTCTGTTGGCTATTAAAGGTTGGTTATCTTTATTCCTATCTACAATCAAGATG
 ACAATGTAATTGAATTATCTTATTATAACACGGTCTGATTCACTGATTACAAGTAGAAAATATGTC
 ATGTTCTCACCTCAAATAAATATGTTGTGCTGTNTGNGTGTCTATATGTTATGTGCGGAGAGGGAGAGTG
 GGGAGGAGAGCAGTGTATCATACATAGAGAGGCTAAATGTCCTACTGTCAGCTTATAAAGGAG
 TTTGACTCCATCCACAGAAGAATGTTTATAAGACTAGGAAAACACGTTGAAAAGTAGGATAAACAGCAACAAAA
 ATCAACTAAATATGTTGTTACTGTTGCTAAGGATTTCTCCTTAGAATAATTAGGATTTAAAAATTCTGTT
 TGCCAAATGCTGTAGATAATGCCAGATTCTCTATCCCTAGGATTCTTATTATTTTCACAGATT
 GAGAACAAAGGGGAGAGATACTGGAAGATAAGATTCCATTAATCTTATAGAAGTGTGAGTGGAGGATAAAGTATTAGACTTTGCT
 CTGCTGTTGAACATGGCATCTTCATAGATTCACTACCCCTATAGCTGGATCTGAAAATTATCTG
 GCCAGATAATTGTCATCTGCTGGATGTTGAGACTGAGATGTGAGTGGAGGATAAAGTATTAGACTTTGCT
 GAGTAACTGCCAACCAAGAAGTATTATCGGACACTACTAGGTGCCTAGGATTGTATCAGAGGAATATGAAAT
 GTGTCCTGCCCTACCTAGTTAACGACAGAATATCTATTAAAGGCTACTTAGCTGAAGGGTAAGGGTGACAGG
 TCTAGGGGAAGCTTGGGAGGTGGTGTGCTGTGACAGAAAAGTGGCAGAGTAGGGACGAGAGACCTGCATTCTA
 GCCCTGTTCTGTCATTGCTCTGTACACTTAGACAACAGCTGACCTCTGAGCTTAGTTCTGAGCTTCTGCT
 AATGAGAGGGTTAGACTACTGAATTGTATGGAAAAAAATACAAATTCTGGCTCTAGGCCATGCCGCTGCTGAAT
 CCGACTGTTCAAGGAAGAGGCTAGGAATCTGTGAGGGAAATCCCCAGGGAAATCTGTGACCAGCCAGGTGTGAA
 ATCTGCTAACTGGAAGATCTAAAGCTCCTTCACCTTGTGATTGTTGCTATGTAACGTTACTGTATT
 CTACGTAATGTGGGTACTTGGATGTTATCATACTGTTCTGTGTTACATACTAATTGTGTAAGAAATGCA
 ATTTAGTCTGTGACCTAACCTGCTGTTCTAGAGGGTTAGTAGTCTTAAATACAAGTAAGACTTA
 AGAGGATATTGATGTTATTACCTGGATATTCTCCCTTTATTATTAAGGAAATTGAGATTCTAGGA
 GCCAAAAAAATGAAAACAAATTCTAAGGCAAAGTTAAAGAAAAAAATTACATTATTCTTACCTGCTACTT
 TATAATGAAAATTAAAAATTATGGAAAGATTCTCTGGATAACAAATCCTGTCTAAAGTAAGAGGTC
 TTTTAAAGTAGGTAGGCTATAAGGCCGTAATTAAATAACTCCTCTAGGGTTGGTGCAATTCTCC
 ATTAATGAAAGATAACATTGAATTCCCCAAAGCAGGTGAGGAGTCGGGGAGGAGAAAGCGATGTTAAATGAAA
 CTCACTGCAAAGAGGGAGGAGAAGGAATGTAACCCCTAAAGCAGATGTGTTGGGCCCTATGAAG
 ACCAGGATTCTGGGGTGTCAAGGGATTGCCCTCTGACAGAGACTAGGGTTAGACTGAGGCTCTGCAAG
 GTGTTCCATTGCCCTCTCGTCCCTCCAGACCTTCTGGGAGAAGAGGTGGGAGGAGGGAGAAAGACTG
 TTCATCTATTCTGAATCTGGAGCAGCTGAAGGTTCTCTGAGTCAGGATGCAGTGGTAATGCATTAAACCAG
 CAAGTGTGCCAAGGATAATGAAAAGGGAAAGGAAGGTCTCTCCCTGATTGTAGCATCCAGCAGTCT
 CTGTAGCCAGGTTACTCAAGAACACATTGATTCTGGCCCTTGCCTGGCAGTGTGATGCCATTATTCTA
 CTGTGTTAAAGTCTCATTATTATTAACATGGTTAGGGAGAAGGGCCACAAATGGAGGGATTGTCTT
 CAAGCACCACAGCTTCAGATAAAATTAGTACTTCAAATATTGTCACCTTAACCTAAATTCTAGAGGGATT
 ATATTGGAGACTCAACTGCCCTGGTTAGTTATAAAATGGCTAGTACTGTGGAATTAAATTAGAAAAGT
 CTTAGCATCAGATCATAAACATTCAAAAAGAACTCACATCCCCTGAAACTCCCAGGGGAGTTGGGATTCT
 TAGTAGATTGGTAGAAAGGGCTCATTCTACTGCACTTCCATTGGTATCTGTTGAGCATGTTTATT
 TTATTCTGTGCTGCAACATCCTATATTATGAGAACATTCTTAAGAAGACCACACATAGAATACCCCTC
 CTATCAGCTCGCTGATTTAGCCTAATTGTTAAATTAGAGATGAATGAAGTGCTGCTGTGAAAGAA
 ATGTACATATACTATTCTGTATCATTAAAATTACATTATTATGGTTCAAG

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FIGURE 48

LGKTGFPNPWEKKKKRREKTVPFL

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FIGURE 49A

CAGCCCGAGCCCGAGCCCGAGCCCGAGCCGGCCACCGCGCCCCGGCCATGGCTTTGCCAATTCCGCCGCA
 TCCTGCGCTGTCTACCTTCGAGAAGAGAAAGTCCCGCAATATGAGCACGTCCGCCGACCTGGACCCCAACG
 AGGTGTGGGAGATCGTGGCGAGCTGGCGACGGCGCTTGGCAAGGTTACAAGGCCAAGAATAAGGAGACGG
 GTGCTTGGCTGCCAAAGTCATTGAAACCAAGAGTGAGGGAGGAGCTGGAGGACTACATCGTGGAGATTGAGA
 TCCTGGCCACCTGCACCACCCCTACATTGTGAAGCTCCTGGGAGCCTACTATCACGACGGGAAGCTGTGGATCA
 TGATTGAGTTCTGTCAGGGGAGCCGTGGACGCCATCATGCTGGAGCTGGACAGAGGCCACGGAGCCAGA
 TACAGGTGGTTGCCGCCAGATGCTAGAACGCCCTCAACTTCTGCACACCAAGAGGATCATCCACCGAGATCTGA
 AAGCTGGCAACGTGCTGATGACCTCGAGGGAGACATCAGGCTGGCTACTTGGTGTGTCTGCCAAGAATCTGA
 AGACTCTACAGAAACGAGATTCTCATCGGCACGCCCTACTGGATGGCCCCCGAGGTGGTATGTGTGAGACCA
 TGAAAGACACGCCCTACGACTACAAAGCCGACATCTGGCCCTGGCATCACGCTGATTGAGATGCCAGATCG
 AGCCGCCACACCACGAGCTAACCCCATGCGGCTCTGCTAAAGATGCCAAGTCAGACCCCTCCCACGCTGCTCA
 CGCCCTCCAAGTGGCTGTAGAGTTCCGTACTTCTGAAGATAGCCCTGGATAAGAACCCAGAAACCCGACCCA
 GTGCCGCGCAGCTGCTGGAGCATCCCTCGTCAGCAGCATCACAGTAACAAGGCTCTGCCGGAGCTGGTGGCTG
 AGGCCAAGGCCGAGGTGATGGAAGAGATCGAAGACGCCGGATGAGGGGGAGAGAGGAGGCCGTGGATGCCG
 CCTCCACCTGGAGAACCATACTCAGAACTCCTCTGAGGTGAGTCCGCCAACCTCAATGCTGACAAGCCTCTG
 AGGAGTCACCTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCAGCCCTCTG
 GGGACAGATCCCTCCAAACCACCAGTCCCCCAGTCGTGGCCCTGGAAATGAGAACGCCCTGGCAGTGCCTGTG
 CCCTGCCGAAGTCCCACCCGTCAATGGATGCCAGAATTCAAGGTAGGCCAGGAGAACGCAAGTTGCTGAGCAGG
 GTGGGGACCTCAGCCCAGCAGCCAACAGATCTCAAAGGCCAGGCCAGAGGCCAACAGCAGGCCCTGGAGA
 CCTTGGGTGGGAGAACGCTGCCAATGGCAGCCTGGAGCCACCTGCCAGGCAGCTCCAGGCCCTCCAAGAGGG
 ACTCGGACTGCAAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCAATCTCCACTGACCTGCTGCTGA
 ACAAAAGAGATGGGCTCTGTCCATCAAGGACCCGAAACTGTACAAAAAAACCTCAAGGGACACGCAAATTG
 TGGTGGATGGTGTGGAGGTGAGCATCACCACCTCAAGATCATCAGCGAAGATGAGAACAGGATGAGGAGATGA
 GATTTCAGGCAGGAACTCCGAGAGCTCGCTGCTCCAGAAAGAGCATCGGAACCAGGCCAGCTGA
 GTAACAAGCATGAGCTGCAGCTGGAGCAAATGCATAAACGTTGAACAGGAAATCAACGCCAAGAACAGATT
 TTGACACGGAATTAGAGAACCTGGAGCGTCAGCAAAGCAGCAAGTGGAGAACGACATGCCGTG
 GCCGCCGGAGGAGGCCAGGGATCCGCTGGAGCAGGATCGGACTACACCAGGTTCAAGAGCAGCTCAAAC
 TGATGAAGAACAGAGGTGAGAACGAGGTGGAGAACGAGCTCCCCGACAGCGGAAGGAAAGCATGAAGCAGAAGA
 TGGAGGAGCACCGAGAAAAGCAGCTCTGTGACCGGGACTTTGTAGCCAAGCAGCAGGAGGACCTGGAGCTGG
 CCATGAAGAGGCTACCACCGACAACAGGCCGGAGATCTGTGACAAGGAGCGCAGTGCCTCATGAAGAACGAGG
 AGCTCCTCGAGACCGGGAGCAGCCCTGTGGGAGATGGAAGAGCACCAGCTGCAGGAGAGGCCAGCTGGTGA
 AGCAGCAGCTAAAGACCAAGTACTTCTCCAGCGGCACGAGCTGCTGCCAAGCATGAGAACGGAGCGGGAGCAGA
 TGCAGCGCTACAACCAGCGCATGATAGAGCAGCTGAAGGTGCGGCAGCAACAGGAAAGGCCGGCTGCCAAGA
 TCCAGAGGAGTGAGGGCAAGACGCGCATGCCATGTACAAGAACGCCCTCACATCAACGCCGGGGAGCGCAG
 CTGAGCAGCGTGAGAACGAGCTCCAGCAGGAGGAGAACGAGGCCAGAAGTGGAGCGGGCTGCCAGCAAC
 AGCAGAACACGAGAACAGATGCCACCTCTGGTAGAGCACGAAACCCAGAAACTGAAGGCCCTGGATGAGGCCATA
 AGAACGAGAACGAGAACGAGCTGCCACCTCTGGTAGAGCACGAAACAGGAAAGGCCCTGGATGAGGCCATA
 ACCTGAAGGAATGCCGGGACAAGCTTCCGCCGCGAAGAAGGCCCTGGATGAGGCCAGAAGAACGAGGCCAG
 AGCAGGAGAGTCTCTCAAGCTGAGCGAGGAGGCCAGTGCCAAACCCCTCCACCCAGCAAGGCCAGGCCAG
 TCTTCCCTACAGTTCTGCGATGCTCTTAACACGCCCGGGCTGTGGCTGCCAGCTGGTGGCCCCAGGG
 CCTTCTCCCTACATTCTGTGAACATGTAACCTCAGGACCCCTTCCCTTGTGCCAGCTCAAATCCA
 GCCCTGCCCTGTGCCACCCACTGTGCCATAGACCTGCCAGCAGCTGCCACTTCTGCTGCCAGCTG
 AGGGTGAGGTGTAATTATTGTACCTGAACCTAATGTATATTCTCCTGAGCCCCAGATCCCTCAAGCTGGAA
 GGGATGGGCTGTTGGTGGGGTCAGGGCCAAGAGGAATGGGTGTTCTGTGGCCTCGAGTCCTCTCTG
 AAAATACCAGTTGCTCTGTGGACAAGCAGCTGCTGATGAAGTCCCCTGGCTCATCCGGCTGGAAATT
 TTGGTTTTCAGCCATTCCCTGAGAGTCAGTCATCATCAAGCTCCACAGCAATTCTGTTCCAGGAGG
 CAGGCCCTGCAGCTGGCTGCTCAGGAGATGCCCTCATCCTCTGTTCTCCAGTTGCTTCCACTTAAGACAA
 GCCTTGCTATGTGGGGGGGGGGACCGGGGAAAGAGGGAGGCTGAAATGTTATTCTGCTTCCGTGTTCA

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FIGURE 49B

TGCCATCTCGCGCCCCCTTCCTGCACATGGGTGTGAATGCACACACATACCGTACACACAGGACTGGTCTGC
TGGCCTGGCCTCTTCTGCCAGGTGGTTGGAACACGTTGCTGCCTGAGCCTGTGCCACTGAGCATGTTAGGTG
GAGCAGTTGGTGTGGCACGTGCGGGGTGTTGGCACCGGAGGCATGGAAAAGCACAGGCTGTACTGCCAGGCTGCG
ATGCGTGTGGCCCCCGCACAGGCTCCTGTGTGCAGGGACTGATTCTCAGCACACGAGGCTTCCACAACCCAGT
CTGCTCCATAGCACTCTGGCCCACCCCTGCTGCAGGTGAAACAGGAGGGCTGTTGCCTCTGCCCATCCCCCG
ACTGTGTTCAAGGAGTCCCACCTTGCATTTCAGACCTGGCTGGCAGTCTGTTGGACTTCTTCAGGAAGAAAAA
GCATCAGGGGGAAATGGAATGCCCTGCCCCAGGAACATGGCAGAACAGGTTCTGTACCTCAGATGGACTCC
TGCTGGGCCTTCGGGGTCTCAGTTGGCTTCCCCCAGATTCTGATTCTACAGCTGCAGAATGTATATAACACAATA
AAAGCAAATGTTGAACCAGT

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FIGURE 50

MAFANFRRIILRLSTFEKRKSREYEHVRRDLDPEVWEIVGELGDGAFGKVYKAKNKETGALAAKVIETKSEEEL
EDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDAIMLELDRGLTEPQIQVVCRQMLEARNFLHS
KRIIHDLKAGNVLMTLEGDIRLADFGVSAKNLKTLQKRDFIGTPYWMAPEVVMCETMKDTPYDVKADIWSLGI
TLIEMAQIEPPHHELNPMRVLKIAKSDPPTLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN
KALRELVAEAKAEVMEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEESPSTPLAPSQSQDSV
NEPCSQPSGDRSLQTTSPVVAPGNENGLAVPVPLRKSRPVSMNDARQVAQEKOVAEQGGDLSPAANRSQKASQS
RPNSSALETLGGEKLANGSLEPPAQAAAPGPSKRDSDCSSLCSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKK
TLKRTRKFVVDGVEVSITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTLQSNKHELQLEQMHKRFEQ
EINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREARRIRLEQDRDYTRFQEQLKLMKKEVKNEVEKLPRQQ
RKESMKQKMEEHTQKKQQLDRDFVAKQKEDLELAMKRLTTONRREICDKERECLMKKQELLRDREAALWEMEEHQ
LQERHQLVKQQLKDQYFLQRHELLRKHEKEREQMQRYNQRMIEQLKVRQQEKARLPKIQRSEGKTRMAMYKKSL
HINGGSAAEQRERIKQFSQQEEKRQKSERLQQQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK
ALDESHNQNLKEWRDKLPRKKALEEDLNQKKREQEMFFKLSEEAECPNPSTPSKAAKFFPYSSADAS

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FIGURE 51A

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FIGURE 51B

GCTCGGGAGGAAGCCCCAGGGCCACCGGGTGTCAAGCCGGCCGACATGCTGAAGCTGCGCTCACTTAGTGAGGGG
 CCCCCCAAGGAGCTGAAGATCCGGCTCATCAAGGTAGAGAGTGGTGACAAGGAGACCTTATCGCCTCTGAGGTG
 GAAGAGCGCGCGCTGCGCATGGCAGACCTCACCATCAGCCACTGTGCTGCTGACGTCGTGCGGCCAGCAGGAAT
 GCCAAGGTGAAAGGGAAAGTTCGAGAGTCCTACCTTCCCCTGCCAGTCTGTGAAACCGAAGATCAACACTGAG
 GAGAAGCTGCCCCGGGAAAAACTCAACCCCCCTACACCCAGCATCTATCTGGAGAGCAAACGGGATGCGCTCTCA
 CCTGTCCTGCTGCAGTTCTGTACAGACCCCTCGAAATCCCACAGTGATCCGGGCGCTGGCGGCCCTGCGG
 CTCAACTTGGGCCTCTCTCCACCAAGACCCCTGGTGAAGCGAGTGGCGAACACACCGTGGAAAGTTGCAACCCAG
 GTGCAGCAGCCCTCAGATGAGAACTGGGATCTGACAGGCACTCGCAGATCTGGCCTTGTGAGAGCTCCGTTCC
 CACACCACCATGCCAAGTACGCACAGTACCGAGCCACTGGAACCCCTCCTAGCAGCCACCAGACCCGAAGAACCAT
 CACATCATCAAGTTGGCACCAACATCGACTGTGATGCTAAGCGGTGGAAGCCCCAGCTGCAGGAGCTGCTA
 AAGCTGCCCGCTTCATCGGGTAACATCCACGGCAACATGCTGAGCCACGTGGCCACACCATCTGGCATG
 AACACGGTGCAGCTGTACATGAAGGTGCCCGCAGCCGAACGCCAGGCCACCAGGAGAATAACAACCTCTGCTCC
 GTCAACATCAACATTGGCCCAAGCGACTGCGAGTGGTTCGCGGTGCACGAGCACTACTGGGAGACCATCAGCGCT
 TTCTGTGATCGGCACGGCGTGGACTACTTGACGGGTTCTGGTGGCAATCTGGATGATCTATGCACTCCAAT
 ATTCCCTGTGATCGGCACGGCGTGGACTACTTGACGGGTTCTGGTGGCAATCTGGATGATCTATGCACTCCAAT
 GCCACCAGGCTGGTCAACAACATTGCCCTGGAACGTGGGGCCCTCACCGCCTATCAGTACCGAGCTGCCCTGGAA
 CGATACGAGTGGAAATGAGGTGAAGAACGTCAAATCCATCGTGCCTGATTACCGTGTATGGAACGTGGCTCGC
 ACGGTAAAATCAGCGACCCCGACTTGTCAAGATGATCAAGTTCTGCTGCTGAGTCCATGAAGCACTGCCAG
 GTGCAACCGAGAGCCTGGTGCAGGGCAGGGAAAGAAAATCGCTTACCAAGGGCGTGTCAAGGACGAGCCAGCCTAC
 TACTGCAACGAGTGCATGTGGAGGTGTTAACATCCTGTTGCAAGTGAGAAATGGCAGCCAAACAGTAC
 CTGGTACACTGCGAGGGCTGTGCCCGCCGCAGCCAGGCCCTGCAGGGCGTGGTGGCTGGAGCAGTACCGC
 ACTGAGGAGCTGGCTCAGGCCCTACGACGCCCTCACGCTGGTGAAGGGCCGGCGCAGCAGGGAG
 GCACTGGGGCAGGCTGCAGGGACGGGCTTCGGAGGCCGGCGCCTTCCCTGAGCCCCCGCCGGCTTCTCC
 CCCCAGGGCCCAAGCCAGCACGTCGCGATTGAGGCCGGACGCCCGCCCTGCCCTGCCCGCAAGGCCCGCG
 GGCCACCAAGCACATGCCCTGGCTGGACCATAGGTCCCGCTGTGGCGAGAAAGGGGTCGGGCCAGCCCTTCCAC
 CCCATTGGCAGCTCCCTCACTTAATTATTAAGAAAAACTTTTTTTTTAGCAAATATGAGGAAAAAAAG
 GAAAAAAATGGGAGACGGGGAGGGGCTGGCAGCCCTCGCCACAGCGCTCCCTCACCGACTTGGCCT
 TTTTAGCAACAGACACAAGGACCAGGCTCCGGCGCGCGGGTCACATACGGGTTCCCTCACCGACTTGGCCT
 CCCGCCGCCGGCGCAGATGCACGCGCTCGTGTATGTACATAGACGTTACGGCAGCCGAGGTTTTAATGAGA
 TTCTTTCTATGGGTTTACCCCTCCCCCGAACCTCCTTTTACTCCAATGCTAGCTGTGACCCCTGTACATG
 TCTCTTATTCACTTGGTTATGATTTGTTTTGTTCTTGTGTTTTGTTAAATTATAACAGTCC
 CACTCACCTCTATTATTCACTTGGAAAACCCGACCTCCACACCCCAAGCCATCTGCCGCCCTCCAG
 GGACCGCCCGTCGCCGGCTCCCGCGCCAGTGTGTGTCGGGGCCGGCCACCGTCTCCACCCGTCCGC
 CGCGGGCTCCAGCCGGTTCTCATGGTGCTCAAACCCGCTCCCTCCCTACGTCCCTGCACCTCTCGGACCAAGT
 CCCCCCACTCCCAGCCGACCCGACCCAGCCACCTGAGGGTGAGCAACTCCTGTACTGTAGGGGAAGAAGTGGGAAC
 TGAAATGGTATTTGTAAGAAAAAAATAAAATAAAATAAAATAAAATTAAGGTTAAAGAAAGAAACTATGAGGAAAA
 GGAACCCCGTCTCCCAGCCCCGGCCAACCTTAAAGGTTAAAGAAAGAAACTATGAGGAAAA
 TGTGAAACAACCCAGGGCCAGGGCCTCACTGGGCGAGGGACACCCGGGGTGAAGTTCTGGGGCTTTATTT
 GTTTGTTGGTTGTTCTCCACGCTGGGCTGCGGAGGGTGGGGGTTACAGTCCGCACCCCTGCACT
 CACTGTCTCTGCCCAAGGGCAGAGGGTCTTCCAAACCCCTACCCCTATTTGGTGAATTGTGAGAAT
 ATTAATATTAAGAAACGGAG

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FIGURE 52

GHP SKP YYA P G A P T P R P L H G K L E S L H G C V Q A L L R E P A Q P G L W E Q L G Q L Y E S E H D S E E A T R C Y H S A L R Y G G S F A E L
G P R I G R L Q Q A Q L W N F H T G S C Q H R A K V L P P L E Q V W N L L H L E H K R N Y G A K R G G P P V K R A A E P P V V Q P V P P A A L S G P S
G E E G L S P G G K R R R G C N S E Q T G L P P G L P L P P P P L P P P P P P P P P P L P G L A T S P P F Q L T K P G L W S T L H G D A W G
P E R K G S A P P E R Q E Q R H S L P H P Y P P A P A Y T A H P P G H R L V P A A P P G P G P R P P G A E S H G C L P A T R P P G S D I L R E S R V Q
R S R M D S S V S P A A T T A C V P Y A P S R P P G L P G T T T S S S S S S S N T G L R G V E P N P G I P G A D H Y Q T P A L E V S H H G R L G P S
A H S S R K P F L G A P A A T P H L S L P P G P S P P P P C P R L L R P P P P A W L K G P A C R A A R E D E G I E L E L F F G T E G P P R P A P
P P L P H R E G F L G P P A S R F S V G T Q D S H T P P T P P T T S S S N S N G S H H S S S A G P V S F P P P P Y L A R S I D P L P R P P S P A
Q N P Q D P P L V P L T L A L P P A P P S S C H Q N T S G S F R R P E S P R P R V S F P K T P E V G P G P P P G P L S K A P Q P V P P G V G E L P A R
G P R L F D F P P T P L E D Q F E E P A E F K I L P D G L A N I M K M L D E S I R K E E E Q Q Q H E A G V A P Q P P L K E P F A S L Q S P F P T D T A
P T T T A P A V A V T T T T T T T T A T Q E E E K P P P A L P P P P L A K F P P P S Q P Q P P P P P P P S A S I L L K S L A S V L E G Q K Y
C Y R G T G A A V S T R P G P L P T T Q Y S P G P P S G A T A L P P T S A A P S A Q G S P Q P S A S S S Q F S T S G G P W A R E R R A G E E P V P G
P M T P T Q P P P P L S L P P A R S E S E V L E E I S R A C E T L V E R V G R S A T D P A D P V D T A E P A D S G T E R L L P P A Q A K E E A G G V A
A V S G S C K R R Q K E H Q K E H R R R A C K D S V G R R P R E G R A K A K A V P K E K S R R V L G N I D L Q S E E I Q G R E K S R P D L G G A
S K A K P P T A P A P P S A P A P S A Q P T P P S A S V P G K K A R E E A P G P P G V S R A D M L K L R S I S E G P P K E L K I R L I K V E S G D K E
T F I A S E V E E R R L R M A D L T I S H C A A D V V R A S R N A K V K G K F R E S Y L S P A Q S V K P K I N T E E K L P R E K L N P P T S I O L E
S K R D A F S P V L L Q F C T D P R N P I T V I R G L A G S L R L N L G F S T K T L V E A S G E H T V E V R T Q V Q Q P S D E N W D L T G T R Q I W
P C E S S R S H T T I A K Y A Q Y Q A S S F Q E S L Q E E K E S E D E E S E E P D S T T G T P P S S A P D P K N H H I I K F G T N I D L S D A K R W K
P Q L Q E L L K L P A F M R V T S T G N M L S H V G H T I L G M N T V Q L Y M K V P G S R T P G H Q E N N F C S V N I N I G P G D C E W F A V H E H
Y W E T I S A F C D R H G V D Y L T G S W W P I L D D L Y A S N I P V Y R F V Q R P G D L V W I N A G T V H W V Q A T G W C N N I A W N V G P L T A Y
Q Y Q L A L E R Y E W N E V K N V K S I V P M I H V S W N V A R T V K I S D P D L F K M I K F C L L Q S M K H C Q V Q R E S L V R A G K K I A Y Q G R
V K D E P A Y Y C N E C D V E F N I L F V T S E N G S R N T Y L V H C E G C A R R S A G L Q G V V V L E Q Y R T E E L A Q A Y D A F T L V R A R R
A R G Q R R R A L G Q A A G T G F G S P A A P F P E P P P A F S P Q A P A S T S R

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FIGURE 53A

ATGGCGCCGCCGCCGCCGCCGTGCTGCCCGTGTGCTGCTCTGGCCGCCGCCCTGCCGGCATGGGGCTGCTACCTAC
CTGCGAGCGGCCGCCCTGGGAGCCGCGCTACCCGGCGGGACCCGCGCCCTCGCCCTCCGGCCGGCTGTACCTAC
GCGGTGGCGCCGCTTGACACCCCCGGCGCCGGGAGCTGCTGGACGTGGGCCGATGGCGGCTGGCAGGA
CGTCGGCGCGTCTCGGGCGGGGGCGCCCGCTGCCGCTGCAAGTCCGCTGGTGGCGCCGAGTGCCCGACGGCG
CTGAGCCGCCCTGCCGGCGCGCACGACCTTCCCGCTGCCGAGCCCGTGCCGCCCCGCTGCCGCTCGCGGAACCGGTGCC
CGGCTCTGCCGGCGCTCTGCTTCCCCGCTCCCAGGCGCTGCCGCGCACGATTCGGCGCTCGCAGCTCCG
ACCACCTTACCGCCCTGCCGCTGCCGCCGCCAGGCCCCGCTGCCGCGCTCCCGCCGATCTGCCCTGCCGCCG
GGCGGCTCGGTCCGCCCTGCCGCTGCTGTGCCCTGCCGCGCGCTGGCGCCGCTGGCGCCGCTGGGACTGGCGCTG
GAGGCCACCGCGGGGACGCCCTCCGCTGCCGACAGGCCCCGGCGGGCACGAGCGGAGGCCGAAGTTCGATGCCAACTAC
CAGGTGGCGTTGTTGAGAACGAAACCGGCCGGCACCCCTACCTCCAGCTGCCACCGCACTACACCATCGAGGGC
GAGGAGGAGCGCGTGAGCTATTACATGGAGGGCTGTTGACAGCGCTCCCGGGCTACTCCGAATCGACTCT
GCCACGGCGCCGTGAGCACGGACAGCGTACTGGACCGCGAGACCAAGGAGACGCCACGTCTCAGGGTGAAGGCC
GTGGACTACAGTACGCCGCCGCTGCCGACCCACTACATCACTGTCTGGTCAAAGACACCAACGACCACAGC
CCGGTCTCGAGCAGTGGAGTACCGCGAGCGCTGCCGAGGAGAACCTGGAGGTGGCTACGAGGTGCTGACCATC
CGCGCCACCGCACCGCACTGCCCATCACGCCACTTGCGTTACCGCGTGTGGGGGCCGCTGGGACGTCTC
CAGCTCAACGAGAGCTCTGGCTGGTGAGCACACGGCGGTGCTGGACCGGGAGGAGGCCGAGTACCAAGCTC
CTGGTGGAGGCCAACGACCAAGGGCGCAATCGGGCCCGCTCAGTGCCACGGCACCGTGACATCGAGGTGGAG
GACGAGAACGACAACACTACCCCCAGTCAGCGAGCAGAACTACGTGGCCAGGTGCCGAGGACGTGGGGCTAAC
ACGGCTGTGCGAGTGCAGGCCACGGGACCGGGCAGGGCCAGAACCGGCCATTCACTACAGCATCCTCAGC
GGGAACGTGGCGGCCAGTTCTACCTGCACTCGCTGAGCGGGATCTGGATGTGATCAACCCCTGGATTTCGAG
GATGTCCAGAAATACTCGCTGAGCATTAAGGCCAGGATGGGGGCCGCCCCCTCATCAATTCTCAGGGTG
GTGTCTGTGAGGTGCTGGATGTCAACGACAACGAGCCTATCTTGAGCAGCCCTCCAGGCCACGGTGCTG
GAGAATGTGCCCTGGCTACCCCGTGGTGCACATTCAAGCGGTGGACGCCAGCTGGAGAGAACGCCGGCTG
CACTATCGCCTGGGGACACGGCTCCACCTTCTGGGGGGCGGCAGCGCTGGGCTAAGAACCTGCCACC
CCTGACTTCCCTCCAGATCCACAACAGCTCCGGTTGATCACAGTGTGCGCAGCTGGACCGCGAGGAGGTG
GAGCACTACAGCTGGGGTGGAGCGGTGGACCAACGGCTCGCCCCCATGAGCTCTCCACCAGCGTGTCCATC
ACGGTGTGGACGTGAATGACAACGACCCGGTGTTCAGCAGCCACCTACGAGCTCGTGAATGAGGATGCG
GCCGTGGGAGCAGCGTGTGACCCCTGCAAGGCCCGACCGTGACGCCAACAGTGTGATTACCTACAGCTCAC
GGCGGCAACACCCGAACCGCTTGCACTCAGCAGCCAGAGAGGGGGCGGCCTCATCACCTGGCGTACCTCTG
GACTACAAGCAGGAGCAGCAGTACGTGTGGCGGTGACAGCATCCGACCGCACACGGTCGACACTGCGCATGTC
CTAATCAACGTCACTGATGCCAACACCCACAGGCGCTGTCTTCAGAGCTCCATTACACAGTGTGAGTCAGTGAG
GACAGGCTGTGGCACCTCATTGCTACCTCAGTGCCAACGATGAGGACACAGGAGAGAACGCCGATCACC
TACGTGATTCAAGGACCCCGTGCCGAGTCCGATTGACCCGACAGTGGCACCATGTACACCATGATGGAGCTG
GACTATGAGAACGAGGTGCCCTACACGCTGACCATCATGGCCCAGGACAACGGCATCCCGCAGAAATCAGACACC
ACCACCTAGAGATCCTCATCCTCGATGCCATGACAATGCACCCAGTTCTGTGGATTCTACCAGGGTTCC
ATCTTGAGGATGCTCCACCCCTGACCAAGCATCCTCCAGGTCTGCCACGGACGGGACTCAGGTCCAATGGG
CGTCTGCTGTACACCTCCAGGGTGGGGACGACGGCGATGGGGACTTCTACATCGAGCCCACGTCCGGTGTGATT
CGCACCCAGCGCCGGCTGGACCGGGAGAATGTGGCGTGTACAACCTTGGCTGGCTGTGGATGGGGCAGT
CCCACCTCCCTAGCGCTCGGTAGAAATCCAGGTGACCATCTGGACATTAATGACAATGCCCATGTTGAG
AAGGACGAACGGAGCTGTTGAGGAGAACAAACCCAGTGGGGTGGTGGCAAAGATTGTGCTAACGAC
CCTGATGAAGGCCATTGCCCAGATCATGTATCAGATTGTGGAAGGGACATGCCGATTCTCCAGCTGGAC
CTGCTCAACGGGACCTGCCATGGTGGAGCTGGACTTGTGAGGTCCGGCGGGAGTATGTGCTGGTGTGAG
GCCACGTGGCTCCGCTGGTGGACGCCACGGTGACATCCTCTCGTGGACCGAGAACACCCGCGCTGTG
CTGCCGACTTCCAGATCCTCAACAAACTATGTACCAACAAGTCCAACAGTTCACCCACCGCGTGTGAC
TGCATCCGGCCCATGACCCGACGTGTCAGACAGCCTCAACTACACCTCGTGCAGGGCAACGAGCTGCCCTG
TTGCTGCTGGACCCGCCACGGCGAACACTGCAGCTCAGCCGCGACCTGGACAACAACCGGCCGCTGGAGGCGCTC
ATGGAGGTGTCTGTGCTGATGGCATCCACAGCGTCACGGCCTCTGCACCGTGTGACCATCATCACGGAC

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FIGURE 53B

GACATGCTGACCAACAGCATCACTGTCCGCCCTGGAGAACATGTCCCAGGAGAACATGCTGGCC
 CTCTTCGTGGAGGGGGTGGCCCGCGTGTCCACCACCAAGGACGACGTCTCGTCTCAACGTCCAGAACGAC
 ACCGACGTCAGCTCCAACATCCTGAACGTGACCTCTCGCGCTGCGCTGGCGCGTCCGCGGCAAGTCTTC
 CCGTCGGAGGACCTGCAGGAGCAGATCTACCTGAATCGGACGCTGCTGACCACCATCTCACGCAGCGCGTGTG
 CCCTTCGACGACAACATCTGCCGTGCGGAGCCCTGCGAGAACATACATGAAGTGCGTGTCCGTTCTGCGATTGAC
 AGCTCCGCGCCCTTCCTCAGCTCCACCACCGTGTCTCCGGCCATCCACCCCATCAACGCCGTGCGCTGCCGC
 TGCCCGCCCGGCTTCACCGGGACTACTGCGAGACGGAGATCGACCTCTGCTACTCCGACCCGTGCGGGGCCAAC
 GGCGCTGCCGAGCCGCGAGGGCGGCTACACCTGCGAGTGCTTGAGGACTTCACTGGAGAGCACTGTGAGGTG
 GATGCCCGCTCAGGCCGTGTGCCAACGGGGTGTGCAAGAACGGGGCACCTGCGTGAACCTGCTCATGGCGGC
 TTCCACTGCGTGTGTCCCTGGCGAGTATGAGAGGCCACTGTGAGGTGACCACCAAGGAGCTCCCGCCAG
 TCCTTCGTCACCTCCGGGGCTGAGACAGCGCTTCACTTCACCATCTCCCTCACGTTGCCACTCAGGAAAGG
 AACGGCTGCTTCTACAACGGCGCTCAATGAGAACAGCACGACTCATGCCCTGGAGATCGTGGACGAGCAG
 GTGCAGCTCACCTCTCGCAGGCAGAACACAACGACCGTGGCACCGAAGGTTCCAGTGGTGTGAGTGACGGG
 CGGTGGACTCTGTCAGGTGAGTACTACAACAAGCCAATATTGGCCACCTGGGCTGCCCATGGCGTCC
 GGGAAAAGATGGCGTGGTACAGTGATGATTGTGACACAACCATTGGCTGTGCGCTTGAAAGGACATCGGG
 AACTACAGCTGCGTGCCTGCCAGGGCACTCAGACCGGCTCAAGAACAGTCCCTGGATCTGACCGGCCCTACTCCTG
 GGGGGTGTCCCCAACCTGCCAGAACAGACTCCAGTGCACAACCGGCAAGTCGTGGCTGCCATGCGGAACCTGTCA
 GTCGACGGAAAAATGTGGACATGGCGGATTATCGCCAACAATGGCACCCGGAAAGGCTGCGCTCGGAGG
 AACTTCTGCGATGGAGGCAGGTGTCAAGATGGAGGCACCTGTGTCACAGGTGAAATATGTATCTGTGAGTG
 CCACTCCGATTGCGGGAAAGAAACTGTGAGCAAGCCATGCCCTACCCCCCAGCTCTCAGCGGTGAGAGCGTCGTG
 TCCTGGAGTGACCTGAACATCATCATCTGTGCCCTGGTACCTGGGCTCATGTTCCGGACCCGGAAAGGAGGAC
 AGCGTTCTGATGGAGGCCACCAAGTGGTGGCCCACAGCTTCCGCTCCAGATCTGAACAAACTACCTCCAGTT
 GAGGTGTCCCACGGCCCTCCGATGTGGAGTCCGTGATGCTGCTCCGGTTGCGGGTGAACGACGGGAGTGGCAC
 CACCTGCTGATCGAGCTGAAGAATGTTAAGGAGGACAGTGAGATGAACGACCTGGTCAACATGACCTGGACTAT
 GGGATGGACCAGAACAAAGGCAAGATATCGGGGGCATGCTTCCGGCTGACGGAAGGAGCGTGGTGGTGGAGGC
 GCCTCTGAAAGACAAGGTCTCGTGCCTGGATTCGAGGCTGCATGCAGGGAGTGAGGATGGGGGGGACGCC
 ACCAACGTCGCCACCCCTGAACATGAACAAACGCACTCAAGGTCAAGGTGAAGGACGGCTGTGATGTGGACGACCC
 TGTACCTCGAGCCCCGTCCCCCAATAGCCGCTGCCACGCCCTGGGAGACTACAGCTGCGTCTGTGACAAA
 GGGTACCTTGGAAATAAACTGTGTGGATGCCCTGTACCTGAACCCCTGCAGAACATGGGGGCTGCGTGCCTCC
 CCCGGCTCCCCCGCAGGGCTACGTGTGCGAGTGTGGGCCAGTCACTACGGGCCGACTGTGAGAACAAACTCGAC
 CTTCCGTGCCCCAGAGGCTGGTGGGGGAACCCCGTCTGTGACCCCTGCCACTGTGCCGTGAGAACAGGCTTGAT
 CCCGACTGTAATAAGACCAACGCCAGTGCCAATGCAAGGAGAATTACTACAAGCTCTAGGCCAGGACACCTGT
 CTGCCCTGCACTGCTTCCCCATGGCTCCACAGCCGACTTGCACATGGCCACCGGAGTGTGCTGCAAG
 CCCGGCTCATGCCGCCAGTGCAACCGCTGCCACTGCAACCCGTTGCCAGGTACACAGCTGCGTCTGTGAAAGTG
 ATCTACAATGGCTGTCCCAAAGCATTTGAGGCCGGCATCTGGTGGCCACAGACCAAGTTCGGCAGGCCGCTGCG
 GTGCCATGCCCTAAGGGATCCGTTGGAAATGCGGTGCGACACTGCAGCGGGAGAACGGCTGGCTGCCAGAG
 CTCTTTAAGTGTACCAACCATCTCTCGTGGACCTCAGGGCCATGAATGAGAACAGTGTGAGGCCAATGAGACGCA
 GTGGACGGGCCAGGGCCCTGCACTGCTGGTGGAGGCGCTGCCAGTGCTACACAGCACACGGCACGCTCTTGGC
 AATGACGTGCGACGGCCCTACCAAGCTGCTGGGCCACGTGCTTCCAGCAGAGCTGGCAGCAGGGCTTCGACCTG
 GCAGCCACGCAAGGACGCCGACTTCACAGGAGCAGTCATCCACTCGGGCACGCCCTCTGGGGCCAGCCACCA
 GCGGCAGGGAGCAGATCCAGCGGAGCGAGGGCGGACGGCACAGCTGCTCCGGCGCTCGAGGGCTACTTCAGC
 AACGTGGCACGCAACGTGCGGGACGTACCTGCCCTCGTCATCGTACCGCCAACATGATTCTGCTGTC
 GACATCTTGACAAGTCAACCTTACGGGAGGCCAGGGTCCCGGATTGACACCATCCATGAAGAGTCCCCAGG
 GAGCTGGAGTCTCCGTCCTCCAGCCGACTCTTCAGACCACCTGAAGAAAAAGAACGGCCCTGCTGAGG
 CGGGCTGGCCGGAGGACCAACCCCGCAGAACACGCCGCCGGGCTGGCACCGAGAGGGAGGCCAGTCAGCAG
 CGGAGGGAGCACCCCTGATGACGCTGGCAGTTCGCCGTCGCTGGTACATATTACCGCACCCCTGGGAGC
 CTGCCCGAGCGCTACGACCCGACCGTCGCAAGCTCCGGTTGCCCTCACCGGCCCATTAATACCCGATGGTG
 AGCACGCTGGTACAGCGAGGGCTCCGCTCCGAGACCCCTGGAGAGGCCGCTGGTGGAGTTCGCCCTG

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FIGURE 53C

CTGGAGGTGGAGGAGCGAACCAAGCCTGTCGCGTGTCTGGAACCACCTCCCTGCCGTTGGTGGGACGGGAGGG
 TGGTCTGCCCGGGGCTGCGAGCTCCTGTCAGGAACCGGACACATGTCGCTGCCAGTGCAGCCACACAGCCAGC
 TTTGCGGTGCTCATGGATATCTCCAGGCGTGAGAACGGGGAGGTCTGCCTCTGAAGATTGTCACCTATGCCGCT
 GTGTCCTGTCACTGGCAGCCCTGCTGGTGGCCTCGTCCTCTGAGCCTGGTCCGATGTCGCTCCAACCTG
 CACAGCATTACAAGCACCTCGCCGTGGCGCTCTCCTCTCAGCTGGTGTTCGTATTGGGATCAACCAGACG
 GAAAACCGTTCTGTGCACAGTGGTGCATCCCTCCACTACATCTACATGAGCACCTTGCCCTGGACCCCTC
 GTGGAGAGCCTGCACTGTCACCGCATGCTGACCGAGGTGCGCAACATCGACACGGGGCCATGCGTTCTACTAC
 GTCGTGGGCTGGGCATCCCGCCATTGTCACAGGACTGGCGGTGGCCTGGACCCCCCAGGGCTACGGGAACCCCC
 GACTTCTGCTGGCTGTCCTCAAGACACCCGTTGGAGCTTGCCTGGACCTGGAGCTGTATAATCATC
 AACACAGTCACCTCTGTCCTATCTGCAAAGGTTCCCTGCCAAAGAAAGCACCATTATTATGGAAAAAAGGGATC
 GTCTCCCTGCTGAGGACCGCATTCCCTGCTGTCATCAGGCCACCTGGCTGCTGGGCTGTCGGCTGTG
 AACCGCGATGCACTGAGCTTCACACTCTCGGACATTCAGCGCTTACAGGGCCCTTCGTCCTCCCTTT
 CACTGCGTCAACCAGGAGGTCCGGAAGCACCTGAAGGGCGTCTGGACAGCAGCTGCAACACCACCTCGGTGACGGGCTGACATG
 TCCGCCACCACCAGGGCCACCCGCTGACGCGCTCCCTCAACTGCAACACCACCTCGGTGACGGGCTGACATG
 CTGCGCACAGACTGGCGAGTCCACCCGCTCGTGGACAGCATGTCAGGGATGAAGGGATCCAGAAGCTCGGC
 GTGTCCTCTGGCTGGTGGAGGGCAGCCACGGAGAGCCAGACGCGTCCCTCATGCCAGGAGCTGCAAGGATCCC
 CCTGGCCACGATTCCGACTCAGATAGCGAGCTGTCCTGGATGAGCAGAGCAGCTTACGCCCTCACACTCG
 TCAGACAGCGAGGACGATGGGTGGGAGCTGAGGAAAAATGGGACCCGGCAGGGCGCCGTCACAGCACCCCC
 AAAGGGGACGCTGTCGCAACACGTTCCGGCCGGCTGGCCGACCAAGGCCTGGCTGAGAGTGCACAGTGAGGAC
 CCCAGCGGCAAGCCCCGCTGAAGGTGGAGACCAAGGTCAAGCGTGGAGCTGCACCGCGAGGAGCAGGGCAGTCAC
 CGTGGAGAGTACCCCCCGGACCAAGGAGAGCAGGGCGCAGCCAGGCTGCTAGCAGCCAGCCCCAGAGCAGAGG
 AAAGGCATCTGAAAAATAAGTCACCTACCCGCCCGCTGACGCTGACGGAGAGCAGCTGAAGGGCCGGCTC
 CGGGAGAAGCTGGCGACTGTGAGCAGAGCCCCACATCCTCGCGACCGTCTCCCTGGCTCTGGCGGGCCCGAC
 TCGCCCATCACAGTCAGAGGCCCTGGGAGGGAGCCGGGGCGTGACCACTCAACGGGTGGCATGAATGTGCGC
 ACTGGGAGCGCCCAAGGCCATGGCTCCGACTCTGAGAAACCGTGAGGCAAGCCGTCACCCACACAGGCTGCGG
 CATCACCCCTGACACCTGGAGGCCAAGGGCCACTGCCCTGAAAGTGGAGTGGGCCAGAGTGTGGCGTCCCCA
 TGGTGGAGCCCCCCCAGCTGATCATCCAGACACAAAGGTCTTGGTCTCCAGGAGCTCAGGGCTGTCAGACCT
 GGTGACAAGTGCCAAAGGCCACAGGCACTGAGGGAGGCAGGACTGGGCCAGCAGGCTGGCCAGAGTTGAGGAACGCCGGGACA
 GACCAAAGACCGCGGTCCAGCCCCGCCAGGCAGCATCTCATGGCAGTGCAGGCCGTCGGCTGGCAGCCGGC
 AGTCCCTTGCAAAGGCACCCCTGTCTAAAATCACTTCGCTATGTGGAAAGGTGGAGATACTTTATATATT
 GTATGGGACTCTGAGGAGGTGCAACCTGTATATATATTGCAATTGTCGCTGACTTGTATCCGAGAGATCCATG
 CAATGATCTTGTCTCTGTCAAGATTGACAGTTGACTTGAATCTGGCATGTGTTGACGAAACTGGT
 GCCCCAGCAGATCAAAGGTGGAAATACGTCAGCAGTGGGCTAAAACCAAGCGCTAGAACGCCCTACAGCTGCC
 TTCGGCCAGGAAGTGAGGATGGTGTGGGCCCTCCCCGCCGGCCCCCTGGTCCCCAGTGGCTGTGTGCGT
 TTGTCCTCTGCTGCCATCTGCCCGGCTGTGAATTCAAGACAGGGCAGTGCAGCACTAGGCAGGTGTGAGGAG
 CCCTGCTGAGGTCACTGTGGGCACGGTGCACACGGCTGTCATTTCACCTGGTCATTCTGTGACCACCA
 CCCTCCCCCTCACCGCCTCCCAGGTGGCCGGAGCTGCAGGTGGGATGGCTTGTCTTGTCTGTCTCCCC
 TGGGACCTGGGACCTTAAAGCGTTGCAAGGTTCTGATTGGACAGAGGTGTGGGCCCTCCAGGCCGTACATAC
 CTCCGCCAATTCTTAACCTCTGAGACTGCGAGGATCTCAGGCAGGGTTCTCCCTCTGGAGTCTGACCAAT
 TACTTCATTTGCTTCAAATGGCCAATTGTCAGAGGGACAAAGCCACAGCCACACTCTCAACGGTTACCAAAC
 TGTTTTGGAAATTCAACACCAAGGTGGGCCACTGCAGGCAGCTGGCACAGCGTGGCCCGAGGGCTGTGGAAAC
 GGGTCCCGGAACTGTCAGACATGTTGATTTAGCGTTCCCTTGTCTCAAATCAGGTGCCAAATAAGTGAT
 CAGCACAGCTGCTCCAAATAGGAGAAACCATAAAATAGGATGAAAATCAAGTAAATGCAAAGATGTCACACT
 GTTTAAACTGACCCCTGATGAAAATGTGAGCAGTGTAGCAGATGCCATGGGAGAGGAAAGCGTATCTGAAA
 ATGGTCCAGGACAGGAGGATGAAATGAGATCCAGAGTCCTCACACCTGAATGAATTATACTATGTCCTTACCA
 GTGAGTGGTCTTCGAAGATAAAAACCTCTAGTCCTTAAACGTTGCCCTGGCCTTCTAAGTACGAAAAG
 GTTTTAAGTCTCGAACAGTCTCCTTCACTGACTTAAACAGGATTGCCCCCTGAGGTGTAATTTTTGTTC

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FIGURE 53D

TATTTTTTCCACGTACTCCACAGCCAACATCACGAGGTGTAATTTAATTGATCAGAACTGTTACCAAAAAA
CAACTGTCAGTTTATTGAGATGGGAAAAATGTAACCTATTTTATTACTTAAGACTTATGGGAGAGATTAGA
CACTGGAGGTTTAACAGAACGTGTATTATTAAATGTTCAAAACACTGGAATTACAAATGAGAAGAGTCTACAA
TAAATTAAGATTTGAATTGTACTTCTCGGGTGTGGTTCTCCACAAACACCCCCGCCCTCCCCATGCC
CAGGGTGGCGTGBAAGGGACGGTTACGGACGTGCAGCTGAGCTGTCCGTGTCCATGCTCCCTCAGCCAGTGG
AACGTGCCGGAACTTTGTCCATTCCCTAGTAGGCCTGCCACAGCCTAGATGGCAGTTTGTCACCAA
ATTGAGGACTTTTTTTGCCATTATTCTTCAGTTCTTCTGCACTGATCTTCCTCTCCTCTG
TGACTCCAGTGAACGTTAGACCTCTGATGTTCCACTGGTCCCTGAGGCTCTGTT

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FIGURE 54

MAPPPPPVLPVLLLAALPAMGLRAAAWEPRVPGGTRAFALRPGCTYAVGAACTPRAPRELLDVGRDGRLAG
RRRVSGAGRPLPLQVRLVARSAAPTALSRRRLRARTHLPGCGARARLCGTGARLCGALCFPVPGGAAAQHSALAAP
TTL PACRCPPRPRCPGRPICLPPGGSVRLRLCALRRAAGAVRGLALEATAGTPSASPSPSPLPPNLPEA
RAGPARRARRGTSGRGSLKFMPNQVALFENEPAAGTLILQLHAYTIEGEEERVSYMEGLFDERSGYFRIDS
ATGAVSTDVLDRETKEVLRVKADVSTPPRSATTYITVLVKDTNDHSPVFEQSEYRERVRENLEVGYEVLTI
RASDRDSPINANLRYRVLGGAWDVFQILNESSGVVSTRAVLDREEAAEYQLLVEANDQGRNPGPLSATATVYIEVE
DENDNPQFSEQNYVVQVPEDVGLNTAVLRVQATDRDQGQNAAIHYSILSGNVAGQFYLHSLSGILDVINPLDFE
DVQKYSLSIKAQDGGRPLINSSGVSVQVLDVNNEPIFVSSPFQATVLENVPLGYPVVHIQAVDADSGENARL
HYRLVDTASTFLGGGSAGPKNPAPTPDFPQIHNSSGWITVCAELDREEVEHYSFGVEAVDHGSPPMSSSTSVSI
TVLDVNDNPVFTQPTYELRNEDAAGVSSVTLQARDRDANSVITYQLTGGNTRNRFALSSQRGGGLITLALPL
DYKQEQQYVLAVTASDGTRSHATAHVLINVTDANTHRPVFQSSHYTVSSED RPVGTSIATLSANDEDTGENARIT
YVIQDPVPQFRIDPDSGTMYTMMELDYENQVAYTLTIMAQDNGIPQKSDDTTLEIILIDANDNAPQFLWDFYQGS
IFEDAPPSTSILQVSATDRDSGPNGRLLYTFQGGDDGDGFYIEPTSGVIRTQRRLDRENVAVYNLWALAVDRGS
PTPLSASVEIQVTIILDINDNAPMFEKDELELFVEENNPGSVVAKIRANDPDEGPNAQIMYQIVEGDMRHFFQLD
LLNGDLRAMVELDFEVREYVLVQATSAPLVSATVHILLVDQNDNPVLPDFQILFNNYVTNKSNSFPTGVIG
CIPAHDPDVSDSLNNTFVQGNELRLLLDPATGELQLSRDLDNNRPLEALMEVSVDGIHSVTAFCTLRTVIITD
DMLTNSITVRLENMSQEKFSLPLLALFVEGVAAVLSTTKDDVFVFNQNDTDVSSNILNVTFSALLPGGVRGQFF
PSEDLQEIQIYLNRTLLTISTQRVLPFDDNICLREPCENYMKCVSVLRFDSSAPFLSSTTVLFRPIHPINGLRCR
CPPGFTGDYCETEIDLCSDPGCGANGRCRSREGGYTCECFEDFTGEHCEVDARSGRCANGVCKNGGTCVNLLIGG
FHCVCPPGEYERPYCEVTRSFPPQSFVFRGLRQRFHFTISLTFTQERNGLLLYNGRFNEKDFIALEIVDEQ
VQLTFSAGETTTVAPKVPNGVSDGRWHSVQVQYYNKPNIIGHLGLPHGPSGEKMAVTVDDCDTTMAVRFGKD
NYSCAAQGTQTGSKKSLDLTGPLLGGVPNLPEDFPVHNRFVGCMRNLSDGKNVDMAGFIANNGTREGCAARR
NFCDGRRQCNGGTCVNRWNMYLCECPLRFGGKNCEQAMPHPQLFSGESVVSWSIDLNIIISVPWYLGLMFRTKED
SVLMEATSGGPTSFRLOQILNNYLQFEVSHGPSDVESVMLSGLRVTDGEWHHLLIELKNVKEDSEMKHLVTMTLD
GMDQNKAIDGGMLPGLTVRSVVVGASEDKVSVRRGFRGCMQGVRMGGPTNVATLNMMNNALKVRVKDGCDVDDP
CTSSPCPPNSRCHDAWEDYSCVCDKGYLGINCVDACHLNPCENMGACVRSPGSPQGYVCECCPSHYGPYCENKLD
LPCPRGWWGNPVCGPCHCAVSKGFDPCNKTNQQCQCKENYYKLLAQDTC

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FIGURE 55

GGCACGAGGGCCCGCGCAGGTCCCAGCCCAGGGCTAGAGACCGAGGGCCGGGTCCGGGCCGGCGGGAC
CCAGGCGGTTGAGGCTGGTCAGGAGTCAGCCAGCCTGAAAGAGCAGGATGGATCTGATGTGGTTAACATGTTG
TGATTGCGGGCGGCACGCTGCCATCCAACTCTGGCATTGTGGCTCATTCTCTGTGGCCTCAGCACTGA
TAAGAATCTATTATTGGTACTGGCGAGGACATTGGCATGCAAGTCGCTATGTCACCATGAAGACTATCAGT
TCTGTTATTCCCTGGGAGGCCTGGCACAAACCCATCCTCATGCTCCACGGATTCTGCCCACAAGG
ATATGTGGCTCAGTGTGGTCAAGTTCCAAAGAACCTGCACTTGGTCTGCGTGGACATGCCAGGACATGAGG
GCACCAACCGCTCCCTGGATGACCTGTCCATAGATGGCAAGTTAAGAGGATACACCAGTTGAGAATGCC
TGAAGCTGAACAAAAACCTTCCACCTGGTAGGCACCTCCATGGGTGGCCAGGTGGCTGGGTGTATGCTGCTT
ACTACCCATCGGATGTCTCCAGCCTGTGTCTGTCAGTACTCAACTGACAATCAATTG
TACAACGGCTAAAGAACCTGCAGGGCTCTGCCGCCGTGGAGAACAGATTCCCTGATCCGTACCCAGAAGAGA
TGAGTGAATGCTTCAGCTGCTCTATGTCGCTCAAGTGCCCCAGCAGATCCTGCAAGGCCCTGTCGATG
TCCGCATCCCTCATAACAACCTTACCGAAAGTTGTTTGAAATCGTCAGTGAGAACATCCAGATACTCTCTCC
ATCAGAACATGGACAAGATCAAGGTTCCGACGCAGATCATCTGGGGAAACAAGACCAGGTGCTGGATGTGCTG
GGGCAGACATGTTGCCAAGTCATTGCCAACTGCCAGGTGGAGCTCTGAAAAGTGTGGCACTCAGTAGTGA
TGGAAAGACCCAGGAAGACAGCCAAGCTCATATTGACTTTAGCTCTGTGACAACACAGACAACAAGA
AGCTGGACTTGAGGGCCCGACTGCAGCCTGCATTCTGCACACACCATCTGCTCCATCCCCAAGTCTGACGCAGC
CACCACTCTAGGATCCTGCCCAAATGCGGTGGAGCGCCAGTGACCTGAGGAAGGCCGTCCCTATCCCTG
GTATCCACGGTCCCCAGAGCTTGGGACCACCGAAAACCTCCAAGATATTTACAAAATAGAAACTCATA
TGGAAACAAAATAAGAAACCCAGCCATGAAATCTACCATGAAGTCTCAAGTTCATGTCAGTGAGAACGTTG
AAAGCAGCCACCTGGACCATAATTAAATCAAGGACATTTCAGACATTCCCTTATAGTTGGAGACTCAAGA
TATTTTGTGATCAGGTGATTCCCTGCATGGGCAGTGGCTTTATAGGAGCATTAGTCCTCATCGCTGAA
CCCTGTTAGGTCTAATTAAAGTTACATAGAGACCCATGTATGACTGCAGCCCATTGGCTGCAAGACCAG
GGAGGAAAGTGGCAAGCTGTAGAAATGTTACACGCATGGAGGGCATTGCTCTAGCCCTCAGAGCGTCCGGAG
CAGCAGGGTACATGGGTGGAGGTTACCGCACCAGTCAGGTATGTTCTGAGTGAACCCACAGCAGTCG
CAGAATGAGCACCTGGCAGGGTGGTTCTAGGAATAATTATTAAAATAGGCTAATAAGCAATA
ATGTTCTAGACATCTGCTAAGTAATCAGACTCAGGTTCCACACACAAGCAACAACACTCGTGGGCCTTTCTAT
TTCAATGTGCTACTAAGAACCTTGGATGTAACATACTAGTTAGTTAATGAATTCTGTGAATTCTGTGAAGAGTA
ATGTGATTGAAAATAAGTCTAACAGCTGTAAAAGTGACCACAATGACATGAAATAATTAAAGTCTAGATC
AGCAAAAAA

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FIGURE 56

MDLDVVNMFVIAGGT LAIPILAFVASFLLWPSALIRIYYWYWRRTLGMQVRYVHHEDYQFCYSFRGRPGHKPSIL
MLHGFSAHKDMWLSVVKFLPKNLHLVCVDMPGHEGTTRSSLDDLSIDGQVKRIHQFVECLKLNKKPFHLVGTSMG
GQVAGVYAAYYPSDVSSLCLVCPAGLQYSTDNQFVQRLKELOQSAAVEKIPLIPSTPEEMSEMLQLCSYVRFKVP
QQILQGLVDVRIPHNNFYRKLFLEIVSEKSRYSLHQNMDKIKVPTQI IWGKQDQVLDVSGADM LAKSIANCQVEL
LENCGHHSVVMERPRKTAKLIIIDFLASVHNTDNNKKLD

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FIGURE 57A

GGAACACAAAAGTGCAGGCCCTGTCTGAAACAGTGGTATCGACTTATCAAAGGTGTAGCCCATCAGTGTATCA
 TGGTTCATGAAGGCTGTCCAGGAAGGAAACATTCACTGGGAGAGCCGTACCTATCCTTATCCTGGAAACCCCAAT
 CACTCAGCGCTTCTGCACAGTGCATGCTATTATGATGCTAATCAGTCTATGTATGTGTTGGAGGCTGTACCCA
 GAGCAGCTGCAATGCTGCTTCAATGACCTCTGGAGACTTGACCTAACAGCAAAGAGTGGATCCGACCTTGGC
 TTCAGGGCCTATCCCTCCCCAAAGCTGGAGCAACTCTGGCGTGTACAAGGACTTGCTAGTGTGTTGGTGG
 CTGGACCGGCCAACGCCCTATCCCTACACCAGCCAGAGAGATTCTTGATGAAATACACACTTACTCACCC
 TAAAAAATGGTGGAACTGCATTGTGACAACCCATGGGCCACCTCCATGGCTGGCACTCCCTGTGTGATAGA
 TGATAAAATGATTGTCTTGGTGGCTTTAGGATCCCAGGAAATGAGCAATGATGTCTGGGTCTTGACCTTGA
 GCAGTGGCGTGGTCCAAGCCAACATCTCTGGCCCCAGTCCTCATCCTCGAGGTGGCAATCTCAGATTGTCA
 AGATGATGCAACTATCTTAATCCTCGGAGGGTGTGGCGGTCCAATGCTCTATTCAAGGATGCTTGGTGTGCA
 CATGCATTCTGGTCTTGGCCTGGCAGCCACTCAAGGTAGAAAATGAAGAGCATGGGGCCCCAGAACACTGTGGT
 CCATCCAGCTGCCGGTGGGACAGTGTGTTGGCTTCAGCCAGGCTCTAGTGGGAGAGCCCCACTCAGGCC
 CAGTTGAACCTCGCCCATCACCTATCAGTGCCACTCCTCCAGCTCTGTTCTGAAACCCGAGAGTACCGCTC
 TCAGTCTCCAGTAAGAACGATGGATGAAGCTCCTGTGTTAACGGCCCTGGGGAAACACTGAGACCCAGGGCTCA
 AAGGCAGACTCCTCAGGTTCCGGGAAGGGAGCCTTCCCCAGCCAGGGAGACGGCTCCTCTATCCTCAATGG
 TGGGAGTTGTCTCCAGGAACGGCAGCTGTGGTGGCTCTTGGACAGTCCTGTACAGGCCATATCTCAAG
 TACTCCATCTGCTCTGAAGGATACGACCTGAAAATAGGACTTTCTTGGCCCCCGACGAGGATCACTACCAGA
 TCAGAAAGATCTGAGATTAGGATCCATAGATCTGAATTGGGATCTGAAACCCGCTCAGTAGTAATCCATGGA
 TGGCATGGACAATAGGACAGTGGGGAGTATGAGACACCCCTCTGAACAGACAAATGGTGTGCATACCCCA
 TCACGTGGCCAGTGCCTTGCAAGGGCCGTCTCCCAGGTGCCCTGCGTGGAGTCTGGAAGCCATAAAGCGAT
 GTCCTCAAAGGCCCTGGCCTCTGCAGCACTAAGTCCTCTTGGCTCTCTCCAGGCTCTGGAGCCA
 GAGTTGAGCAGTGGAGAAACAGTGCCCATCCCTGCCAGGGCTGCCAAGGAGATGGACATTCTTACCTCC
 CATTGCTGCCGCTGGCCACCACCCCTCACAGTCCCTAAATGTTGGCAAACCCCTATACCAGAGTATGAACTG
 CAAGCCCATGCAGATGTACGTGCTGGACATTAAAGACACCAAGGAGAAGGGCGGGTCAAATGGAAAGTATTAA
 TAGCAGTTCTGTGGTGGACCTCTGAAACCAGCCTGCATACCGTGGTACAAGGCAGGGTGAACTCATCATATT
 TGGAGGACTCATGGACAAGAACAGAAATGTAAGTACTATCCAAAACAAACGCCCTGTACTTGTACGAGCAA
 GAGATAATGTGTTCTAAACCCCTTCCTTCTGTGGCTTTAATTGGAATTTCAGTGTGTAAGCATTGGA
 CTGAGAATTGGAAAACAAATTACTCCCAGAAGCCAAAACCTTTAATTCCAACCGAAGTCACTCCAGGCTGG
 GATCAAATCTCATTAAAGAAAAAAATTATATAATATATATATATATTATAGCCAACCTGTGACAA
 AAAAGGGAGAGATTCCATCTGGTTCAGATAAAAGTTGTGTTAACAGGGCTGGCTGCCTTTTC
 TACCTGCTGGTAACTAGACCAAGAAGTTAGAGAATAGACTAACATCAGTAACCTCCAAAAGAAACTGAAGAGC
 CCCCTGAAATCTTATGTGCCCTCTGGAGTTAAAATGAAAGGGCATATGTAAGTTGCAAAGGTGGAGGGT
 TTAGACTCTCATGCTTCAGGTGCTGCCAGGGTAAAGTAACCTGTTTCCCTCTTAAACCCACAGAGGAC
 CTGTGACAGCTGCAGAAATGCCAGTGCCTGCCCTCTGCCTTATGGCTGAGGAAGTTACCCAAACAAA
 GGATTATTCCACATTGTGTGCCGGTCATTGTGAAATAATGTTATGCAGCCAACATCTGACCGCTAGTAG
 TGTCCATTGGTCTTGGAGTGTCTTGTGTCTCAGAAAACATTGTGCTGATTGTGAAATTCTGACAA
 TCAATCATATTGGTGGCAAGTTGCCAAAAACATATTATTCTCCTCTTCTCCCTTAGAACATGGTACTTGG
 AAAC TGCCCTTCCATTCACTTACAGGCTGTTTCTTCTACCTTTCTTTCTTTCTTCTCATATG
 TGGTAAGTCTAAACCTGCTGACTTCTGTTTACAAAGCTCAGGTGCCCTACAGAAATCAGAACAGTGC
 TTAGAAATACTTGTGGAACCCCTTCCCTGGTCACTAGGGGGCAGTAGGGAATTCTAAGATGCCAATATTGTG
 AGAAATCTTGAAGCAAGCATCAAAGATACTGTTTCCCTATGGCTTCTTTACTTCAAAGCACATTGA
 GCACACTCATCCCATATTGTAGAATGTGGAATTGATTCTGGAAGGAATTCCAATAACAGTTCTTTAGAAA
 TGTTTTCTTGTGGTACATATTCCTCTGGTATTGGCAGGTGATGGAGTTGAGAATCATGTACTT
 GACTTCTTGACGCATGGCTGACCTCAGAAACAGCTCCATCCTTGCACCTGTCTTCTCATGTGTCACCCAAATA
 GGGCTGGGTTTACTTCACCTCATTCTGAGATTAAGGTGTAACCAAGTAGAGCATTTCTGCTGATACA
 GAAAGTTACTAGTCTCAACCATGCCCTGGCATAGGAGATGTCAAATAAGTTATTCAAATGGCACCAATTAA
 ATAGGGATTGGTATTCTCATCAGTGGAAAGAGGATTGGTGTGCTTGTGAAATTAA
 TCCTAATTCAAACATCACCTGCCACCCCTGACACTCCTCTTTATTAGCGTTCTCAGGCACAAAGCCT

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FIGURE 57B

GCTGCAGCTGGCCCTGGGTCTGGCTTCAGCCAGCATCTGGCAGCCTAAGTGTACTGATAAGTGTGTTCTCC
TGTTACATCATGCTGAATCCTTCCCTAGCCATTAGCTTTATGATGTGGCTTCGTAGGAAAGCCACCTGGT
GCCAAGCCTAGCTTGTGGGGAGGGTATGTGTCAGAAACTGCTCTTGTGTTCCATGAGGAAACAACA
TGTGTCTACTTATGTGGCATCCAACCTGCTGGAGCTCCACACTCCCTTCGCGACTCAGGCTCTGGTGTGTT
CCAATCCTTGCTGGCAAAGACTGTCGATCATGTGGGTCTTATTACAAGGAAAGCTGGGCCAGAAGGCTA
GCAATTCAAGGTGTTACCGCTATTGCTGTACCTTGTGTTAGGACATTGTGTTGTGCACTGGACTGTGCCTCCAAAC
TCAGTAGTTCCTATCTAAATATAAAGTATATTAGAAACCTGAAAGTACAGAATCTCAACCTTACAGTCTTCCCT
TAGTCCTGTGGCCTCCTAAGCCAGCTTAACTGTTGATTCCACTTCCCCAAGTAGGCAGGAAACAGA
TATGTTGATTGTCTAGAAAGTAATCTGGTCCTGAACTCCATTGAATTCCAGTTGACCCATACTGCCTGGA
ACCAGACTGTTGCTTACAGCTTTAAGAAAAATCTGCCTGTCTGCCCTTATTATGGTTGGTCTTGGTAGCTC
CTGGGCACTGTGGCGTGTACCATGGGAAAGTGAATTCAACACAGTGAAGGTGATTGTCTCCTCAGGCCTCCTGAA
GCCACCTGTGCGGTGGACTTCACGTCTCGGCCAAGGCAGACATTCCACAATGCCGTGGATGCTGCAGTCAG
GCCAGATTGAACCATGACCCCATTTCACATGATACCAATTGTCTTAAATTCACTGAGAAAAATGAGACTA
AATTTTTTTAACCCCTCAGGAGCACCTGAAGCAAATATTATCCGTATTATTGAAAATTCAATTGTTCTACT
TGAAGCTTTAACCCCTTCCATTCTGCAAGTGTGCCCTTGAGAGCTCCATGCCCTAGTGAATTCACTGGTCAC
CTTGTCCATCTTACTTAAGAATTCTAGTCTCTCCCTACCCCTTGTGGACAGAGCTTCTGTTCTTATTACAG
GTTATACAGCAGAGCGGGTTTGTGTTCTTCAATTCCACCCCTCATTGGTTGGTAGCTCCACAACCTC
ACCCCTACACTTGGAGCACAAATTGGTGTGAAACAAGCTTAAATTCAATTAGGGCATACTGGGCT
TACTCTCTCCCAGCTGTGGATTGATTGATTTAATGTTGAGTTTACAGCAACAGCTGAAAACCATGA
ACTATTCTAGGAACGTGTGGAACTCTTAAAATAAGAAAAGAGGAGGAGGAGGAGGAAGAAAGAAAACCAAC
TTAAGAACCTGACTTGGAGGACAGAAAGCCACCAGCCAATGGAGAACAAAGAGATGTTCCCTTCCCTTCT
TTCACCTGTCAATTGGTTCTCTGCTTCACTCTTCTCCCCCTTAAAGTGGTATTCTGGTCTT
GTCTGTCTGCTTGTGCTTGTGGTATCCTGGCATGGTATGCTCCACTTGCATTATCCATGGTCTTAC
CAGCGACAAGTCAGTGGGGAGGATCTAACACACGCCCTGGTGGAGGAAGCTGAATTCCAGGCCTGCGTCCCAT
GTAGCCTCTCCATGAACCTGCAAGGCATGTTGCACTGGTTACAGTAAGTGGCTCCCTCACCGTGTTCATT
GTCAAATGAGAGCAAACCTTGGTGTGGCTCCATTGTACACTCTACTGCTCTGCTCCCCCTCCCTCAACCAGG
GTTCATGTCAGTGCACACCCCATGTGCCCTGGCGAAGCTGGTGTGAGTGTGTTCCCATACAACTCAGGGA
TGCCAGGTGGCTTACCCCTGAGATAGTCATTGGCACATAACAGTGTAGGAATGAAACATGGATTCAATTGATA
TTAAATCTGTCAATTCAATTGGTTAATGTTCCCTGATGACTTTAGCAATTAAACAATAATGGA
CAATTGTCTAAC

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FIGURE 58

EHKTAALVCKOWYRLIKGVAHQCYHGFMKAVQEGNIQWESRTYPYPGTPITQRFSHSACYYDANQSMYVFGGCTQ
SSCNAAFNDLWRLDLNSKEWIRPLASGSYSPKAGATLVVYKDLLVLFGGWTRPSPYPLHQPERFFDEIHTYSPS
KNWWNCIVTTHGPPPMAGHSSCVIDDKMIVFGGSLGSRQMSNDVWVLDLEQWAWSKPNISGPSPHPRGGQSQIVI
DDATIILGGCGGPNALFKDAWLLHMHSGPWAQPLKVENEEHGAPELWCHPACRVGQCVVFSQAPSGRAPLSP
SLNSRPSPISATPPALVPETREYRSQSPVRSMDEAPCVNGRWGTLRPRAQRQTPSGSREGSILSPARGDGSPILNG
GSLSPGTAAVGGSSLDSPVQAISPSTPSAPEGYDLKIGLSSLAPRRGSILPDQKDLRLGSIDLNWDLKPASSNPMD
GMDNRTVGGSMRHPPEQTNGVHTPPHVASALAGAVSPGALRRSLEAIKAMSSKGPSASAALSPPPLGSSPGSPGSQ
SLSSGETVPIPRGPAQGDGHSLPIARRLGHHPPQSLNVGKPLYQSMNCKPMQMYVLDIKDTKEKGRVKWKVFN
SSSVVGPPETSLHTVVQGRGELIIFGGLMDKKQNVKYYPKTNALYFVRAKR

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FIGURE 59

GCTCTGGCGGCTCCCGCGCTCCGGCTGGCGCTCGGGCCCTGCACCTGTGACTCTCGGCCGCTGCCCTCG
GCCCGCCGGCGCCGCAGCCCCATGGCCCCGTCCAGGCTGCAGCTCGGCCCTCGCCGCCTACTCCGGCATTGAG
CTCCGTGGCCGGCTTCTCATCTTCTCGTCTGGACGGTGGCTACCGACAGCCGGGACCGCGGCCATGGGAGG
GCTCGCAGGGGTGCTGGCACTGTGGGTCTGGTGACGCACGTGATGTACATGCAAGATTATTGGAGGACCTGGCT
CAAGGGGCTGCGCGCTTCTTCGTPGGGGTCTTCTCGGCCGTCTCCATCGCTGCCCTTCGACCTTCT
CGTGCCTGGCCATCACCCGGCATCAGAGCCTCACAGACCCCACCAGCTACTACCTCTCCAGCGTCTGGAGGCTTCAT
TTCCTCAAGTGGGCTTCCTGCTCAGCCTCTATGCCCACCGCTACCGGGCTGACTTTGCTGACATCAGCATTCT
CAGCGATTCTGACCCAGGGGTGAGGTCTGCAACCTGGGGGGCTTAGGACCTGGACTCAGCCTCTGAGAT
GTTGGGAGAGGCTACTCCCACCCCTGGTGACCCAGAACTGTGGCAGAAAATACACAGCAGGACGAGTGTGGTC
TCCCAGGAAGCTGCTCTGCCGTCCCCTTCGAGGAAACCTGAGTGTGGTAGAGAGGGGATCCTGCCATGTTGCT
CCTCATCAGCCTGGCCAGAGGGCAGCTTAGACCTTTCAAATGAATCTGTTCTTTCTTTTTTTTTTC
TTTTTTTTTTTGAGATGGAGTCTTACTCTGTCACCCAGGCTGGAGTCAGTAGTGGCATCTCAGCTCACT
GCAACCTCCGCCTCCCAGGTTCAAGCAATTCTCCTGCCCTCTCAAGTAGCTGGATTACAGGCATCTGCC
ACCATGCCGGCAAATTGGTTAGTAGAGACAGGGTTTGCCATGTTGCCAGGCTGGCTCGAACCTCC
TGATCTCAGGTGATTACCCGCCTCAGCCTCAAAGTGTGGATTAGGTGTGAGCCACCGTGCCCCGGCCTG
GATCTGTTCTTAGCACGCAGTGAGGAATCTTGTACTTAAGGCCAGGGCAACAAAGTCAAGAGGTCAAGGTGT
AGGGCCATGAGGCCTGGACCTATGCTGCAGGCAAGGGTTCCATCCCCGCTGCCCTAGGCACTCTTCCAAAGG
CCAGGTTGGGACCTGGGAGGTCAAGTCAAATCTAGCAGAGACCTCTAAACCCCCATCCCAGCACCCCC
TCCTGTTGTCAGAGCTGGCTCCCATGAGTGTGCTAGAGCCAGATAGCCGTGGCCCCCACCACATCTCACTC
ACACACACAGGCATCCATACACCCAGAAGACTTCCCAAATGAGGCCAGACTCAGGGTCACGGGAATGTGCTTC
TGCCCCCTGTAAGGGCTTGGGAAGGGCAACATAGTAGAGGCTGGAAAGAGCCCCAACCTGTGCCATGCC
CCTCCAGCCCTGCGTTCCATTCTGCCCTCTCAGAGTGCCCTGCTGCACCCAGACCACGGCCAGGAGAGACCT
TCTCTCCACTCCAGCCCTCTCACTGCCCTCAACTAGAGCTTCACTTACATTCCCTCTGAAGGACA
CAAATCTGTTCTGCCATACACTGCCCAAGGGCTCACCTAACCTGGGAGGGAAAGGGCTGGTACAAGG
ATGATTCTGTTAGGCTGCCATTGACGGTCTCCCCCTCCCCATCTGATGTGTCCTGCCCTCAGCTTTG
CCTTATCTGTCAGTCACCTAGCAAAATACAGCGGCCATTGTATCAAAAAAAAAAAAAAA

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FIGURE 60

MPTATGLTLLTSASSAISDPGGEVSAPWGLRTWTQPLRCWERLLPPPGDPRTV AENTQQDECGLPGSCPAPRLS
RKPECREGILPCCSSSAWPEGSFRPFQMNLFSFLSFFFFLRLWSLTLSRLECSSAISAHCNRLPGSSNS
PALASQVAGITGICHHARQIFVFLVETGFCHVGQAGLELLISGDSPASAFQSAGIIGVSHRARPGSVFLARSEES
LYLRPGQQSQEVKV

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FIGURE 61

ATGGGTGTGCTGGATAGCCGGTTGCACCTGTTCTGGGTCTCTCTCTGTTCCACTGTTCCACTTCAGGAGA
 GCCAAGCATCTCACCCATGCTCTCATATTCACTAGTCAGGCATCCTACCCAAGTATCCTAATTATAAAACTAGCCACC
 AGCTCAGGCTCTGTATCCCAGTCACCACCCCCATTCAAGGCCCAACTATCCAGTGCAGAGGCCCTCAGGTGCA
 GAGGGCCAGTTCAAGCCAAACCAGGACAGACCCAGCCACCCCTGTTCCAGGCCAGCTACAAGCCTCTGAAACC
 CACCAAGTCTGATGGTAGCCTCCCTCCCTGTTCTCCAGGAAGAAGAGAAATGCCCTCCCTCCAAAACCAAGCC
 CAACCAAGAAACCTGTCCCCACCCCCCTCATCAGCTCTCCAGATCCGAATGGGATTGCAAGAGTCTGAGCAGT
 GGTGGTTGGTGGGCAGCAACAGGCCCTTGCAGCAGCTGGACGGATGGGGTGGGGCGAGGTCTGGGCCAGGG
 CCTGAGGGTACGGGACTAAGGCCAGGCCAGCGTCGCTCCGGCCCTCTCCACGCCACGCCAGGCCAGCAGGCTCCA
 CGGCTCCAGGAGTTGCCCGCCTAGCTGCCCTCCCTGCCTCGCTTGAGCTCTGAGCTTCAACCTGACC
 TATGGTGCCCTGGTCACCCAGCTATGTAAGGACTATGAAAATGATGAAGATGTGAATAAACAGCTGGACAAAATG
 GGCTTAAACATTGGAGTCGGCTGATTGAAGATTCTTGGCTCGTCAATGTTGGAGGTGCCATGACTTCGG
 GAAAATGCCGATGTCATTGCCAAGGTGGCCTCAAGATGTACTTGGCATTCAACTCAAGCATTACTAATTGGAGC
 CCAGCTGGTGAATTCTCCCTCATTTGAAAATAACCCCTGGTGGACTTGTGGAACTTCCCTGATAACCAC
 TCATCCCTTATTATTCCAATCTCTTGTGTTGGGGAGCTTGGAGATGGTCCAGATGGCTGTGGAG
 GCCAAGTTGTCCAGGACACCCCTGAAAGGAGACGCCCGCAGGGGGCGCCGGAGGCCCTGCCGCCGGCG
 CGCGGACCCCGGACCCCAACGCCGCCGCCAGCCCGGACGCCCTGCCGGAGGCCCTGCCGCCGGCG
 CTCGAGGGCGGGAGCGGCCGCCGGCGCCGCCAGGCCCTGCCCTGCTGGAACCTTCCCAGGCCCTCC
 GACCTGAAAGCCCAGCCCTCTGCTGCCGCTGCTGCCGCCACACGAGGGTAGCCGAGGCCAGGAATCT
 TGGCAGGGCGTGGGGAGGCAGCGGGTGGCGCTCCGGAAAAGGCTGCAATGCGAACCAAGAGCACGTC
 ACGGACGCCATGCTGGGACTCTGACACCCCTGCTTCGCTGCTGCTACTGGTGTGGCTGGGTGT
 GGGCCGCGGGCGTCTCTGGGGCGGGCTGGAGGGCTATGCCCAAGTGAAGTACATCCAGGCCATG
 CAGAAAGGACCTGTGGGACGCCCTCCGTGAGGGCAAAGGCCAGTACCTGAAATGCCCTACCGCTGCTGCC
 ATGGACCTGAAGGGAGAGGCCGCCCTGGGAAGGCCGGCTCGGGTCCCGGCTGGGCCCCCTGGCTTCTCCGGATG
 GGAAAACCAGGCATGGGAAAGCCAGGACTCCATGGGAGCCCTGGCTGGGCCCCCTGGCTTCTCCGGATG
 GGCAAGGCTGGTCCCCCAGGGCTCCCTGGCAAGGTGGGCCACCAGGGCAGCCGGGCTTCGGGGGAGCCAGGA
 ATACGAGGGGACCAGGGCTCCGGGACCCCCCAGGACCCCCCTGGCTCCGGGCCCTCAGGCATTACTATCCCT
 GGAAAACCAGGTGCCAAGGGTGCCAGGGCCCCCAGGATTCCAGGGGAACCAGGGCCCCAGGGGGAGCCTGG
 CCCCCAGGTGATCGAGGCCTCAAGGGGATAATGGAGTGGGCCAGGCCGGCTGCCCTGGGGCCCCAGGGCAGGG
 GGTGCCCTGGGCCCTGGCTCCAGTGGCTTAGGCAAACCTGGTTGGATGGCTTCTGGGCC
 CCAGGAGACAAGGGTAGCTGGGCCCTGGAGTTCCAGGCCAGGGGGAGCCAGGAGCTGTGGGCCAAAA
 GGACCTCTGGAGTAGACGGTAGGGAGTCCCAGGGCAGCAGGGTGGCAGGACCACAGGCCATCAGGGCC
 AAAGGGGAGCCAGGGACCCGGGCCCCCTGGCTGATAGGCCACTGGCTATGGATGCCAGGACTGCCAGGC
 CCCAAGGGGACAGGGGCCAGTGGGTCCAGGACTCTGGGGGACAGGGTAGGCCAGGGAGGATGGGAG
 CCAGGGGAGCAGGCCACAGGGCTTGGGGCTCCCTGGACTTCCCTGGCTGCAAGGGCTTCCAGACGT
 GGGCCCCCTGGGCCCTAAGGGTAGGGCAGGGCCTGGAGGACCCCCCAGGAGTGCCTGCCATTGAGGTGACCAGGG
 CCTAGTGGCCTGGCTGGAAACCAGGGTCCCAGGTGAGAGGGACTTCCTGGGCCATGGACCCCCCTGGACCA
 ACTGGGCCCAAGGGTAGCCGGGTTTCACGGCTGCCCTGGAGGACCAAGGGTGGCAGGAGCCCTGGGCCAGAAA
 GGTGACTTGGGCTCCCTGGCAGCCTGGCTGAGGGTCCCTCAGGAATCCCAGGACTCCAGGGTCCAGCTGGC
 CCTATTGGGCCCCAAGGCCCTGCCGGCTGAAGGGGAACCAAGGCCCTGCCAGGGCCCCCTGGAGAGGGAGAGCA
 GGGGAACCTGGCACGGCTGGGCCACGGGCCCCCAGGGTCCCTGGCTCCCTGGAAATCACGGGCCCTCCGGGG
 CCTCCCGGGCCCCCGGACCCCCCTGGTCCCTGGGCCCTGGATGAGACTGGCATCGCAGGCTGCACCTGCC
 AACGGCGGTGTGGAGGGTCCGTGCTGGCAAGGGGGCAAGGCCACAGTTGGCTGGCGAGCTGTCTGCC
 GCCACACCGGCCCTCACTGCCGTGCTCACCTGCCCTCCCCGCCATGCCGTGAAATTGACCGGACT
 CTCTACAATGGCCACAGCGGCTACAACCCAGCCACTGGCATCTTCACCTGCCCTGTGGCGCGTCTACTACT
 GCTTACCATGTGCAAGGGCACCACAGTGTGGGTGGCCCTGTACAAGAACACAGTGCAGGCCACCTATACC
 TACGATGAGTACAAGAAGGGTACCTGGACCAAGGCATCTGGTGGGGCCGTGCTCCAGTGCAGGCCAACGACCA
 GTCTGGGTGCAGATGCCGTGGACCAAGGCCAACGGCCTACTCCACGGAGTACATCCACTCCTCTTTCAGGA
 TTCTTGCTCTGCCACTAA

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FIGURE 62

MGVLD SRLHLFLGSSLLFPLFHFRRAKHLTHALIFSLGILPKYPNYKLATSSGSVSQSPPPFRPPTIQCQRP SGA
EGQFSQTRTDPATLVSSPAYKPPETHQSDGSLPSLFSQEEREIASLQNQAQPETCPHPLISCSQIRMGFAEV LST
GGWWAATGPLRGSWTDVGARS GPGPEGTGTKA EASPPGASPTATAERAPRLQEF AALAASPCVRVLSSELF TL T
Y GALVTQLCKDYENEDDVNKQLDKMGFNIGVRLIEDFLARS NVGRCHDFRETADVI AKVAFKMYLGITPSITNWS
PAGDEF SLILENNPLVDFVELPDNHSSLIYSNLLCGVL RGALEMVQMAVEAKFVQDTLKGDAARGGRQSDAEP RRR
RGPRPTTPPAQPRTPPLPGALAARAALEGRERRPAAAPAGPASAGTFPGPSDLKAQPLLLPLPPPRVAAEAQES
WQAWGGSGWRVALRKRLQMRT RSTSTDAMLGTLTPLSSLLLLVLVILCGPRASSGGAGGAAGYAPVKYIQPM
QKGPVGPPFREGKGQYLEMPLPLPMDIKGEPPGKPGPRGGP GPGFPKGPKGMGKPGHLHGQPGPAGPPGFSRM
GKAGPPGLPGKVGPPGQPGL RGE PGIRGDQGLRGPPGPPGLPGPSGITIPGKPGQAQGVPGPPGFQGE PGQGE PG
PPGDRGLKG DNGVGQPGLPGAPGQGGAPGPPGLPGPAGLGKPGLDGLPGAPGDKGE SGPPGVPGPRGE PGAVGPK
GPPGV DGVGVPGAA GLPGPQGP SAKGE PGTRGPPGLIGPTGYGMPGLPGPKGDRGPAGVPG L LGDRGE PGEDGE
PGEQGPQGLGGPPGLPGSAGLPGRGGPPGPKGEAGPGGPPGVPGIRGDQGP SGLAGKPGVPGERGLP GAHGPPGP
TGPKGE PGFTGRPGGPVGAGALGQKGDLGLPGQPGL RGP S GIPGLQGPAGPIGPQGLPGLKGE PG LPGPPGEGR A
GEPGTAGPTGPPGVPGSPG ITGPPGP GPPGAPGAFDETGIAGLHL PNGGVEGA VL GKGKPQFGLGELSAH
ATPAFTAVLTSPFPASGMPVKFDRTLYN GHSGYNPATGIFTCPVGGVYFAYHVHVKG TNVWVVALYKNNVPATYT
YDEYKKGYLDQASGGAVLQLRPNDQVWVQMPSDQANGLYSTEYI HSSFSGFLLCPT

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FIGURE 63

GTTGCCGCTGCGCACCTGGCTCAGGTGAGCTGCCCGCCCCGGCGAGCCCCAGGTCTGGCAGCAGCC
CCTGACCTGTCCAGGTGCCCTGTCCAGCTGACTGCAAGGACAGAGAGGAGTCTGCCAGCTCTGGATCAGTCT
GCTGGCCGAGGAGCCGGTGGAGCCAGGGTGACCTGGAGCCAGGCCAGCTGCCAGGAGGCCGGCTCAGAGC
CATGCCAGGTGTCTGTGATAGGGCCCTGACTTCCTCTCCCCGTCTGAAGACCAGGTGCTGAGGCCTGCCCTGGG
CAGCTCAGTGGCTCTGAACGTGACGGCTGGTAGTCTCTGGGCCCCACTGCTCCCTGCCCTCAGTCCAGTGGCT
GAAAGACGGGCTTCATTGGGAATTGGGGGCCACTACAGCCTCCAGCAGTACTCTGGTCAAGGCCAACCTGTC
AGAGGTGCTTGTGTCAGTGTCTGGGGTCAACGTGACCAGCACTGAAGTCTATGGGGCCTCACCTGCTCCAT
CCAGAACATCAGCTTCTCCTCCTTCACTCTCAGAGAGCTGCCCTACAAGCCACGTGGCTGCCGTGCTGCCCTC
CCTCCTGGCCTGCTGCCCTGCTGGCCGCCCTGCTATGTCAAGTGCCTCAACGTGCTGCTGGTA
CCAGGACCGTATGGGGAGGTGGAGATAAACGACGGGAAGCTCTACGACGCCACGTCTCACAGCAGTGGCC
CGAGGACCGCAAGTCGTGAACTTCATCCTAAAGCCGAGCTGGAGCGCGCTGGGCTACAAGCTTCTGGGA
CGACCGCGACCTCTGCCGCGCTGAGCCCTCCGCCACCTTGGTGAACCTGAGCCGCTGCCGACGCCCTCAT
CGTGGTGCCTCGGACGCCCTCTGAGGCCGGCTGGTGCAGCCACAGCTCCGGAGGGCTGTGCCGGCTGCT
GGAGCTCACCGCAGACCCATCTTACACCTTCAGGGCCAGAGGCGCGACCCCGCGCACCGCGCTCCGCCT
GCTGCCAGCACGCCACCTGGTACCTTGCCTCTGGAGGCCGGCTCCGTGACTCCTCCGATTTTG
GAAAGAAGTGCAGCTGGCGCTGCCGCGGAAGGTGCGGTACAGGCCGGTGGAGGAGACCCAGACGAGCTGCA
GGACGACAAGGACCCATGCTGATTCTCGAGGCCAGTCCCTGAGGCCGGGCTGGACTCAGAGGTGGACCC
GGACCCCTGAGGGCGACCTGGGTGTCGCCGGGCTGTTTGGAGAGCCATCAGCTCCACCGCACACCAGTGGGGT
CTCGCTGGGAGAGAGCCGGAGCAGCGAAGTGGACGTCTGGATCTCGGCTCGCAAACACTACAGTCCCCCACAGA
CTTCTACTGCCTGGTGTCAAGGATGATATG**TAG**CTCCCACCCAGAGTGCAGGATCATAGGGACAGCGGGGGCC
AGGGCAGCGCGTCGCTCTGCTCACAGGACCAACCCCTGCCAGCAGCCCTGGACCTGCCAGCAGGCC
TGGGAAAAGGCTGTGGCCTCAGGGCGCTCCAGTGCCAGAAAATAAGTCCTTGGATTCTGAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 64

MPGVCDRAPDFLSPSEDQVLRPALGSSVALNCTAWVSGPHCSLPSVQWLKDGLPLGIGGHYSLHEYSWVKANLS
EVLVSSVLGVNVTSTEYGAFTCSIQNISFSSFTLQRAGPTSHVAAVLASLLVLLALLAALLYVKCRLNVLLWY
QDAYGEVEINDGKLYDAYVSYSDCPEDRKFVNFIILKPQLERRRGYKLFLDDRDLLPRAEPSADLLVNLSCRRLI
VVLSDAFLSRAWCSHSFREGLCRLLELRRPIFIITFEGQRRDPAHPALRLLRQHRHLVTLLLWRPGSVPSSDFW
KEVQLALPRKVRYRPVEGDPQTQLQDDKDPMLILRGRVPEGRALDSEVDPPEGDLGVRGPVFGEPSAPPHTSGV
SLGESRSSEVDVSDLGSRNYSARTDFYCLVSKDDM

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FIGURE 65A

GGAGCTGGGGATCCCCGCTCCCTGGACCCCAATGACATGGTCTCATGAGCGTCCCTGACTGCCTCAGCCTCAT
 GACCTATGTGCCCAGTATTACAACCACTTCTGAGTCAGTCTGGCCAAGCTGGTCTGCCACCCAGAAAGGGCT
 TGCACCCCTGTTCCCGCCGCTGTAGCACCCACTCCAGTGGAAATCAGAAGATGTGGCTCAGGGCAGGAGCTCTC
 CTCAGGCAGCCTGTAGAGCAGGGCACCGGCCAGACCCCCAGCAGCACGTGCGCAGCCTGCCAGCAGCATGTGCA
 CTTGGTGCAGCGTACCTGGTGCAGGCAGGCTGACCGCAGGCTGACCGCAGTGGCTGAGAGCAGCACGTGCGCAGCAGCAG
 CCTGCTCCCTGGGGCTTATGAGAATGGGCTGAGGAGGGCACCTTGTGAGAGCAGAACACTGTGCCAGGCTGG
 CCCGGGGACACGGTCGGGACCAGGCCTGGGCCCTCTCACAGCCAAAGCAGCAGCACCCAGCAGCAACTCGCAGA
 AGATGCCAAGGATGTTCCAGGAGGCCAGCTCCAGTGTCTGCAGGGCTGAGGCCATGGACCCAAGGC
 CAGCCCTGAGGCCCGCGCAGATCCCTACCAAGCCCCGGGCTCTGCCAAACTACAGGAGCTGGCCAGCCCC
 TGCGGGCCGCCCCACCCCTGCCCTCAGGAAGGCCCTGTAGAGCACCACCCAGCACCCCCCACGCCCGGCC
 CTCCAGTCTGCAGCAGGAGAACCTGGTGGAGCAGGCTGGCAGCAGCAGCTGTGAACGGAGACTGCACGA
 ACTGCCTGCCCCAAGCCAGGGGACACCGAAGCCGTCGAGGGGACACCAGCCCCAGGAAGGACCCCCATGGAT
 CACGCTGGTGCAGGCAGAACCAAAGAAGAAGCCAGCCCCACTTCCCCCAAGCAGCAGCCCAGGGCCACCAAGCCA
 GGACAGCAGGCAGGGTGGAGAATGGAGGCACCGAGGGAGGTGGCCAGGCCAACGGCCAGCCTGGAGTCAA
 ACCCTATAACCCCTTGAGGAGGAGGAGGACAAGGAGGAAGAGGGCTCCAGCTGCACCCAGCCTGCCACCA
 CCTGCCCTGGCCACCCGGAGTCCACACCCAAGTCCCTGCACCCCTGGTACGGCATCACCCCTACCAGCAGCCC
 CAAGACAAAGAAGGCCCTGCCCGCGCAGCCTGGCTCTCCACGGCTCTCCACGCCCTCCGCCCTCGA
 CTCGGAGGCCCTCGGCCACACCATGCCAGCGCTCAGCGTGGAGAGCCTGCTGAGAGCGCCAGCCAGAC
 TGCAGGTGCAGAGCTCTGGAGGCCAGCTGTGCCAAGAGCTCTCAGAGCCTGCTGTCCATGCCCTGGTAC
 CCTGGAAACCTGTCAGCCTCTTACCAACTCCTCCCTGGCTCTGGGAAACTAGTGGAGCCTAGAGTGG
 ACAAAATGCCTCAAGCCAGCCCTGGCCTGCCAGGACCAGGGCAGCTCAGGCCCCAGCCAGCAAGCC
 CAGTGGGCCACCCAAACGCCCTCTTGTGGAGACAGGAGGCCCTGGCTCTCCCTGGAAAGCTCGTCCCC
 ACAGCTGCAGGTAAGTCCCTGCAAGGAGAACCTTTAACCGGAAGCCATCACCTGCAGCGTCCCCAGCCAC
 AAAGAAGGCCACCAAGGGATCCAAGCCAGTGAGGGCACCTGCCCTGGACACGGCTTCACTCATAAACGCAA
 GGTCCAGGCTGACCAAGTACATCCCTGAGGAGGACATCCATGGAGAGATGGATACCATTGAGGCCGGCTGGATGC
 CCTGGAGCACCCTGGGTGCTGGAGGAGAACAGCTGCGTGGCCCTGAATGAGGGCGTGAGGATGACATGCT
 GGTGGACTGGTCAAGCTCATCCACGAGAACGACCTACTGGTGCAGGAGTCCGAGCTCATCTATGTTCAA
 GCAGCAGAACCTGGAGCAGGCCAGGCTGATGTCAGTATGAGCTCCGGTGCCTCCTCAATAAGCCAGAAAAGGA
 CTGGACGGAGGAGGACCAGGGCCGGAGAACGGTGTGATGCAAGGAGCTTGTGACCCCTATTGAGCAGCGCAACGC
 TATCATCAACTGCCCTGGATGAGGAGCCGGCAGAGGGAGGAAGAGAACAGATGTTGGAAGCCATGATCAAGAA
 GAAAGAGTCCAGAGGGAGGGCTGAACCTGAGGGCAAGAAGAAGGGGAAGTTCAAGACCATGAAGATGTTGAA
 ACTGCTAGGAAACAAAGTGTGATGCCAAGAGCAAGTCCCCAGAGACAAGAGTAACAGCAGGAGAACCCAGTTGGG
 CTGCCCTCCTGGAGCAGCTCTGGCTGTGCTCTGGTGAAGGGGGCCCTGCTCCCTCAGATCAGTCAGG
 AGGAAGATGACTAAAGGGAGGGATCCTCTGGGTGATGCCCTTCCCTCAGGGACCTCTGACTGCTCTGG
 AAAGAATCTCTGTTCTCCAGGCCAGGCAGCGGTATTGAGCCCTGCCAACCTGATTCTGATGACTGC
 GGATGCTGTGACGGACCCAAAGGGCAAAATAGGGTCCCAGGGCCAGGGAGGGGCCCTGCTGAGCACTCCGCC
 CTCACCCCTGCCAGCCCCCTGCCATGAGCTCTGGCTGGTCTCCGCCCTGGCTCTGCTCTCCAGGCAGGCC
 AGCAAGTGGCGCTGGGCCACACTGGCTCTCCCTGCCATCCCTGGCTGAGTCTCTGCTCTCCCTGCTG
 CAGGGCCCTGGATCTCAGTTCCCTCACTCAGGAACCTGTTCTGAAGTCTCAGTTAAGTTGAGTTATG
 ACTGAGTGGCTGTACTGTCAGACGTGAATGGGCTGACGGCAATCCATCCCTCTCCCTCACAGTTCCAGG
 AGCGGCTCCCTCGTCTCCCTACTCACAGGGAGCCCTTGCAGGACCAGGGCTGCGACGGCCATGCTGG
 GGCAGGTGAGTGTCTGTTAGCTGCTCCAGTGTGTCAGGCTGAGTTCTGGTCCCTGGTTGTCAGGTAGG
 AAGGGTGCACCTGAAAGCAGGTGCTCATCTGGTCTTAACGTTATAGTCTGACCCCTCACTTACGGCTTCC
 TGCCACCCCGGTCCAGGGAAAGAGGCTCGCTCCGCCATGGTCATCACTGGTCTGTCTGCTCTGGTCT
 TTCCCTGACTCCCTCCCACCGAAGGCCATGGCTGATGGCTACTCACCCCTCTGGATGGCTATGGGAGAGGAGG
 GGGGACCGCCACCTTCTGAGGAAATGTGCCAGCAGCTTGGTCAAAGCAGTGTGCTATAAGCTATCTCT
 GGGATGCCTCTAGGCCCTTCCCTACACACCTCTGGAAAAGATTACACTGTATTAACCTCGAGGAGTT
 CTCACCAATAAACAGACAACCTCAACTGCCAGTGCCCTGCAGCCTCGGCCACAGCGGCAGCCTGTTGCC
 TT

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FIGURE 65B

CCACCTGCCTCTGCCACACCTGGTGGCTGAACATCTCTGGTCGCCAGAGGCCATGTTGGGCCATCCTCCAAGA
GGGATCTGCCCTCACCGCTGCCACTGGCAGGATCCCTTCCTCTGCAGGGAGAGGTGGCTCCTCGGCCATG
CAGCCCCCTGGCAGGCTCTAAACATGCCTGTGACCTGGAGCTGGGCCACCAACTCCAGGGCCTTCCAGG
GCCAGACAGGTAAACACGCATGAACCCAGTGACAGCTCTGACGGGCTGTTGGTGTCAAGGAGACAAAGCTGGCA
GGGGCAGGGGTGAACGGAGGCAAGTCAGTCACCTGTGGCTGTGGGCTGAATGTGGGCCGGTGTGCCAGA
TCCTTGTCTAAAGAAGCTAGAAATCCAGATTTATGTGTGTGAATTGTAATGCTAAAGCTAGCCTGAATT
TTTTTTTTTTTGAGACAGAGTCTCGCTCTGTCGCCAGGCTGGAGTCAGTGGCGCATCTCAGCTCACTGC
AGGCTCCGCCCTGGGTTCACGCCATCCTGCCCTGGCCTCCTGAGCAGCTGGACTACAGGCGCATGCTAC
GACGCCCTGGCTAATTTGTATTTAGTAGAGACGGGTTCACCGTGTAAACCAGGATGGTCTCGATCTCCT
GACCTTGTGATCCACCCACCTGGCCTCCAAAGTGCTGGGATTACAGGCGTGAGCCACCACGCCGGGACTAG
CCTGAATTCAATCAAGGGTGGCTGATACTGTGTGTCAGGGTGGACTGGATTGTCCTGGGGGTTCTGGT
TTGCTGCCCTGACCACATGATGGGCCCTCGAGGTCGAGGACAACCTGTTCCATTAGATTGCACCCCTGCC
TCAGGTTCTTGAGGGTGTGGACACAGAGGCTTCCATGGGATGTCCTGAGGCCGCCCTGATTGGGCCCTCA
CCATTTACAGGGCCGTTTATTCTGAAACCGAAACTGGGTCATGTGACCTGATGGGATTATGGGACTCCCTCC
AGGTGCCCGAGACAAGGTGATAATTCAAAATATTGGTGTATTAGGGACAAGCAAATGACAGAATACCGG
AGAAGGCAGGGATCGTGGGTGCAGGAGCCAGAGGGGAGGGGACAGATGTGCTGTACAGGACAAGGTGTCAG
GTGACTCCTCCCAGCAGGGCTCGCAGATGCAACAGCACGGAGCTGGGGTTTGCCTAGAAAGGTACGCG
GCACATGCAGGGATTGAACTCCCAGGGCAGGGCTCTAGGTCGCTCCACCTTTCATGTTCTTGTGGCCA
TGGGTATAGTGGAAAGACATAAGCTAAAGCCAACCTTTAACCTGAAATGCACTGCTTGCAGGTAAATGCCCT
GGTTGGTATCTTGTGAGACTTAGTTTACAGAGGATAATGAACCGTTGCAGAGGTTATTGAGATCATTA
ACAGAGTGGATTAGCACCTGCCACTGCACTCCAGCCTGGCGACAGAGCAAGACTCAGTCATGAAATTGCC
AAATTAGCTGGCAGGGATGGTGTGGCTGTAATCCTAGCTACTTGGGAGGCTGAGGCATGAGAATTGCC
GAACCCAGGAGGTGGAGGTTGCACTGAGCCGAGATCGTGCCTGACTCCAGCCTGGGTGACAGCGCGAGACTC
CGTCTCAAAAAAAAGCTGGGTGAAAAACACCTGTGGTCCCAGCTATTCTGGAGACTGAGGAGGAGGATTGCTT
GAGCTCAGGAGTTCTGGCTGCAGTGGCTATGATCATGCCACTGTATTACAGAATGGGTGACAGAATGAGAGCGA
CACTGTCTCAAAAAAAAGGCCGGAGCGGTGTTGTGCCTGTAATCCCAACACTTGGGAGGC
CAGGGTGGCGGATCACTTGAGGCCAGGAGTTCAAGACCAGCCTGGCCAACATGGTAATCCCATCTACTAA
AAAAATTAACTGGACATGGTGGTGGACACTTGTAAATCCCAGCTACTCAGGAGGCTGACACATGAGAATTGCTTGA
ACCCGGGAGGCAGGTTACAGTGAGCCGAGATAGCACCACACTCCAAACCTGGCACAGAGTAAGGCTCTGT
CTT

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FIGURE 66

ELGIPALLDPNDMVSMSVPDCLSIMTYVSOYYNHFCSPGQAGVSPPRKGLAPCSPPSVAPTPVESEDVAQGEELS
SGSLSEQGTGQTPSSTCAACQQHVHLVQRYLADGRLYHRHCFRCRRCSSLLPGAYENGPEEGTFVCAEHCARLG
PGTRSGTRPGPFSQPKQQHQQQLAEDAKDVPGGPSSAPAGAEADGPKASPEARPQIPTKPRVPGKLQELASPP
AGRPTPAPRKASESTTPAPTPRPRSSLQQENLVQEAGSSSLVNGLHELPVPKPRGTPKPSEGTPAPRKDPPWI
TLVQAEPKKKPAPLPPSSSPGPPSQDSRQVENGTEEVAQPSPTASLESKPYNPFEEEEEDKEEEAPAAPSLATS
PALGHPESTPKSLHPWYGITPTSSPKTKRPAPRAPSASPLALHASRLSHSEPPSATPSPALSVESLSESASQT
AGAELLEPPAVPKSSSEPAVHAPGTPGNPVSLSNSTNSSLASSGELVEPRVEQMPQASPG LAPRTRGSSGPQPAKPC
SGATPTPLLVGDRSPVSPGSSSPQLQVKSSCKENPFNRKPSPAASPATKKATGSKPVRRPAPGHGPLIKRK
VQADQYIPEEDIHGEMDTIERRLDALEHRGVILLEKLRGGLNEGREDDMLVDWFKLIHEKHILLVRRESELIYVFK
QQNLEQRQADVEYELRCLLNKPEKDWTTEEDRAREKVLMQELVTLIEQRNAIINCLDEDRQREEEEEDKMLEAMIKK
KEFQREAEPEGKKKGKFKTMKMLKLLGNKRDAKSKSPRDKS

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FIGURE 67

CTTTGTTTGCTTCGAGATGGCTGCGGGGATGTATTGGAACATTATCTGGACAGTATTGAAAACCTTCCCTTG
AATTACAGAGAAACTTCAGCTCATGAGGGACCTAGACCAAAGAACAGAGGACCTGAAGGCTGAAATTGACAAGT
TGGCCACTGAGTATATGAGTAGTGCCCCCAGCCTGAGCTCCGAGGAAAATTGGCCCTCTAACACAGATCCAGG
AAGCCTATGGCAAGTGCAAGGAATTGGTACGACAAGGTGCAGCTGCCATGCAGACCTATGAGATGGTGGACA
AACACATTGGCGGCTGGACACAGACCTGGCCCGTTTGAGGCTGATCTCAAGGAGAACAGATTGAGTCAAGTG
ACTATGACAGCTCTCCAGCAAAGGAAAAAGAACGGCCGACTCAAAGGAGAACAGCTGCTCGTGCCTGTT
CCAAAGGAAAAACTCGGATGAAGAACCCCCAAGACTGCCAGAAGAACGTTAAAGCTCGTGCACAGTCCTG
AGTATGGATGCCCTCAGTGACCTTGGCAGTGTCACCCCTCTGATGTGTTGGATATGCCCTGTGGATCCAAACG
AACCCACCTATTGCCCTTGTCAACCAGGCTCCTATGGAGAGATGATTGGCTGTGACAACCCCTGATTGTCATTG
AGTGGTCCATTTGCCCTGTGTGGGCTGACAACCAAGCCTGGGGAAATGGTTTGCCACGCTGCCAGTCCTG
AACGGAAGAAGAAATAGATAAGGGCCTGGATTCCAACACAGTTCTCACATCCCTGACTGGCTAGTGGG
CAGAGGAATGCCCTGTCTGGGCCAGGGGTTCAAGGGAGGAGTGGATGGCACAGTGTGTCATCCCTCTCC
CTCTCCCCACTCCCGGTGCTGAGGCTGCATCAGACCCCTGGTAGGGAGGGTGCAGCCACTAACGGTATGTG
TCTCCTTCAGCCCTCTCCTCGGAGGGACGTGGCTTGCCCAGTGTCTTGCCTCATGCTGAGGTCGGTGCT
GTATTCAGAGGGAGGGTCTTTCATTCTCTTGTGTTGTTGATTTAAGGACTGGGCATAGCATGGGGCAGTCC
CCCAGACCTCTTCATTCCCCCTCTGTGGTGAGGGCTAGGTGTGATCAACACTTTCTCCATTCCCTCTG
CTTTTTCATGGTGGGATCCACCAGGTCACTAGCTCTGCCCTAGTTGAAGGGCACCCCTCTGTGCCAA
GAGGATTCACTCTGGAGAGGGGCAAGGTGGAATGCAGATAACTCACATGTAAAAGGAACCTGGTAGGTAAAT
AAAAGCTATACATGTTGAAAAAA

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FIGURE 68

MAAGMYLEHYLDSEIENLPFELQRNFQLMRDLDQRTEDLKAEIDKLATEYMSARSLSSEEKLALLQIQEAYGKC
KEFGDDKVQLAMQTYEMVDKHIRRLDTDLARFEADLKEKQIESSDYDSSSSKGKKGRTQKEKKAARARSKGKNS
DEEAPKTAQKKLKLVRTSPEYGMPSVTFGSVHPSDVLDMPVDPNEPTYCLCHQVSYGEMIGCDNPDCSIEWFHFA
CVGLTTKPRGKWFCPRCSQERKKK

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FIGURE 69

TACGTGAAGCACCGACACAAACTGGAGAATGGCTGGCTGGCTCAGTCCCTAACGCAAGGGCTCCATGGAGGCT
GGCCCTTACCTGCCCGAGCCTGCAGCAGCCTCTGGAACAGCTGACTCGGTATGGCGGCTCCTGGAGGAGCTC
CTGAGGGAAAGCTGGGCTGAGCTCAGTCTGAGTGCCTGGGGCTGTACAGCTGCTCCGGAAACAA
GAGGCCGTGGCAGAGACCTGCTGGCCGTGGAGGCCGTGCGTGGCTGTGAGATAGATCTGAAGGAGCAGGGACAG
CTCTGCATCGAGACCCCTACTGTCACTGTGCCGAAAGAAGTGCCTCGCCATGTCTTCTTCGAGCAT
CTCCTCCTGTTCAAGCTCAAGGCCCTGAAGGGGGTCAGAGATGTTGTTACAAGCAGGCCCTTAAGACT
GCTGATATGGGCTGACAGAAAACATCGGGGACAGCGGACTCTGTTGAGTTGTTGGGTTCCGGCGCGGTGCA
CGAGAGGCATACTCTGAGGCAACCTCACCAAGAGATCAAACCTCAAGTGGACAAGTTCTATTGCCAGCTGCTG
TGGAGACAGGCAGCCCACAACAAGGAGCTCGAGTGCAGCAGATGGTGTCCATGGGATTGGAAATAACCCCTC
CTGGACATCAAAGCCCTGGGGAGCGGACGCTGAGTGCCTGCTCACTGGAAGAGCCCAGAAACACTTGACTCT
TCTGGAGATGTGCCCCAGGACCAAGAACAGCCCAGCCTGCAACCCCCCACCCTGGGAGCAGCACTCCCACC
CTGGCCAGTCGAGGGATCTAGGGCTATCCCGACAGAGTCATGCTCGAGCCCTGAGTGACCCCACCAGCCTCTG
TGACTTGGAGAAGATCCAGAACTTGCCTGCAGCTCTCCTCTCAGCACACTTGGGCTGGGATGGCAGTGGGCA
TAATGGAGCCCTGGCGATCGCTGAATTCTCCCTCTGCTTCCGGACACAGAGGAGGTCTAACGACCAGAGTA
TTGCCCTGCCACCACTATCTAGTCTCCCTAGCTTGGTGCCTCTCCTGCAGGAGTCAGACCAGCCACATTGCT
TGCCTTCATACCCCTGGAGGTGGGAAGTTATCCCTCTCCGGTGTTCCTCCATCTGGCCACTGTATCCAGGAC
ATCACTCCCATGCCAGCCCTCCCTGGCAGCCATGTTCTCCCTTTCTCACCCCTGACTTCCCTGAGAAGAA
TCATCTCTGCCAGGTCAACTGGAGTCCCTGGTACTCCATTCTGAGGTGTACAAGCAATGAAGCTATGCAAACA
ATAGGAGGGTGTGACAGGGAAACCGTAGACTTATATGTAATTACTGTTATTATAACTATTGTTATATTAA
ATGTATTACTCACACTTGCCTCT

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FIGURE 70

MEAGPYLPRALQOOPLEQLTRYGRLLEELLREAGPELSSECRALGAAVQOLLREQEARGRDILLAVEAVRGCEIDLKE
QGQLLHRDPFTVICGRKKCLRHVFLFEHLLLFSKLKGPEGGSEMFVYKQAFKTADMGLTENIGDGLCFELWFRR
RRAREAYTLQATSPEIQLKWTSSIAQLLWRQAAHNKELRVQQMVSMGIGNKPFLDIKALGERTLSALLTGRAPET
LDSSGDVSPGPRNPSLQPPHPGSSTPTLASRGILGLSRQSHARALSDPTTPL

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FIGURE 71

CTTTCTGCCCGACTCCCACAGCTACACCATGCAGGAATTGCCCGGCGTTACTCCGGAGGTCCCAGGCCTTGCT
GGGCCAGACTGATGGAGGTGCCGCAGGAAAGGACACGGACAGCCTGGTGCAGTACACCAAGGCTCCCATCCAGGA
GTCGCTCCTCAGCCTCAGTGTGAGCAAGCTGGCTGTAGCCAGCTCCTGCCCTGATGCCGTTATGGG
TGACCAGTCCAAGCCCCGGGCAAGGATGAGATGGATCTGCTCTATGAACTGCTGAAGCTGTGCCAGCAGGAGAA
GCTGAGGGATGAGATTACTGCCAGGTTATCAAGCAGGTACGGGACACCCCCGGGAACACTGCACTGAGG
CTGGAGCTCCTCAGCCTCTCACAGGCTTCTCCCCCGTCGACCAGGCTGATGCCCTACCTGACCAAGTTCT
GCAGGATTCAAGCCCCAGCCAAGAGCTGGCCGGAGCAGCCAGGAGCACCTCAGCGCACAGTCAAATATGGGG
GCGCCGGCGGATGCCCTCACCGGGTGAATGAAGCTTCTGAAAGGACAAGCAGATTGCCGTGCTTATTCA
CCTGCCGGGGGTGTGGATTAGGACAAATCCAGACTTCACAGTAGCAGCAGAAGTGCAGGAGGAGCTGTG
CCGGCAAATGGGTATCACGGAGCCTCAGGAAGTGCAGGAATTGCCCTTCTCATCAAAGAGAAGAGCCAGCT
GGTGCGGCCCTGCAGCCGCCAATGCCAACAGCGTGGTAGTGGACCAGGACGTGAGCCTGCACAGCCGGCG
GCTCCACTGGGAGACCCCCACTGCACTCGATAACTCCACCTACATCAGCACCCACTACAGCCAGGTGCTGTGGGA
CTACCTTCAGGGGAAGCTGCCAGTCAGCGCAAGGCAGACGCGCAGCTGCCAGGCTGGCCGCCCTGCAGCACCT
CAGCAAGGCCAACAGGAATACCCCCTCAGGGCAGGACCTGCTAGCTAACGTGCAAAGCAGCTGCAACGGCAGGT
GAACACGGCCTCCATCAAGAACCTGATGGTCAGGAGCTGAGACGGCTGGAAGGACACAGCCCCCAGGAAGCACA
GATCAGCTTCATCGAGGCCATGAGCCAGCTGCCCTCTCGGCTACACCGTCTATGGGTGCTGCGAGTGAGCAT
GCAGGCCCTGTCCGGACCCACTCTCTGGGCTCAACCGCCAGCATCTCATCCATGGACCCCAGCTCCAGAG
CCTGTACTGCCGCATTGCCCTGAAGAGCCTGCAGGGCTCCACCTGCTAACGCCCTGGAGGAGAAGGGCCCC
TGGCCTGGAAGTCAACTATGGCTCAGCTGACAACCCCCAGACCATCTGGTTGAGCTGCCACAGGCCAGGAGCT
GCTATAACCAACTGTCTCCTGATAGACAGCAGTGCCTTTGCACTGAGTGGCCCAGCATCAACTTGAGAGGAGT
CAGGCCGGGAGAGAAGAGGATGAGGCCCTCCCCGGCCAAGTCTCACCCACATGGTCTGCCCTGGATGCTATCA
GATCACTGTTCTAGAACCTGCCCTCAGCACGCCAGGCCACATGCAGGCCATGAGGCAAGGGCTGCTATCA
CGTCACCAGCAGGCAAAGAAAACAGCCAGACCCCTCCAGGACGGCTGGGGCCAAGCAGGCTGAGGAACCTCG
GCTGGGGCACCTGAGGTTGCCAGTCTGAGGGAGATGCCACCCGACCCCAGGCTCCGCCAGGCCACATTAG
ACAAGCCCAGGCATGGAGAAACAGCTGCTGAGGAAATAAAACTCCCTGGAGAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAA

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FIGURE 72

MQE FARRY FRR SQ ALL GQT DGG AAG KDT DSI LVQ YT KAP IQE SLL SLS DDV SKL AVAS F LAL MRF MG DQ SK PR GKD EMD LLY ELL KLC QQ EKL RDE IYC QVI KQVT GH PR PE HCT RGWS FLS LLT GFF P PSTR LMP YLT KFL QD SGP SQ EL ARS SQ EHL QRT V KYGG RRRM P P GEMKA FLKG QAI RLLI HLP GGV DY RT NI QT FT VAA E VQ EEL CRQ MGITE PQ EV QEF ALF LIKE KSQL VRPL QPAE CLNS VV DQD VS LHS RRLH WET PLH FDN STY I ST HYS QVL WDYL QG KLP VS AK ADA QLAR LA ALQ HLS KAN RNT P SG QD LLA YVP KQL QRQ VNT ASI KNL MGQ EL RR LE GH SP QEA QIS FIE AM SQ LPL FG YTV GVL RVSM QAL SGPT LLG LNR QHL I LMD PSS QSL YCRI ALK S LQR L HLLS PLE EKG PPG LEV NYG SA DNP QTI WFEL PQA QEL LYTT VFL IDSS ASCT EWP S IN

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FIGURE 73

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FIGURE 74

MALETPTPGPPREGQSPASQAGTQHPPAQATAHSQSSPEFKGSLASLSDSLGVSVMATDQDSYSTSSTEEELEQF
SSPSVKKKPSMILGKARHRLSFASFSSMFHAFLSNRKLYKKVVELAQDKGSYFGSLVQDYKVYSLLEMMARQTSS
TEMLQEIRTMMTQLKSYLLQSTELKALVDPALHSEELEAIVESALYKCVLKPLKEAINSCLHQIHSKD GSLQQL
KENQLVILATTTDLGVTTSVPEVPMMEKFLQKFTSMHKAYSPEKKISILLKTCKLIYDSMALGNPGKPYGADDF
LPVLMYVLARSNLTEMLLNVEYMMELMDPALQLGEGSYYLTTYGALEHIKSYDKITVTRQLSVEVQDSIHRWER
RRTLNKARASRSSVQDFICVSYLEPEQQARTLASRADTQAQALCAQCAEKFAVERPQAHRLFVLVDGRCFQLADD
ALPHCIKGYLLRSEPKRDFHFVYRPLDGGGGGGGSPPCLVVREPNFL

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FIGURE 75

ACGAGGGACGCAGCC**ATGGCGGAGGC**GGCTTGGAAAGCCGTGCGGAGCGAGTTACGAGAATTCCCGCCGCTGCA
 AGGGAGCTCTGCGTGCCTCTGCTGTGCCCTACCTGGACAAACCCCCAACTCCGCTCCACTTCTACCGGGACTGG
 GTCTGCCCAACAGGCCGTGCATTATCCGCAACGCTCTGCAGCACTGGCCGCCCTCCAGAAGTGGTCCCTCCCC
 TATTCAGAGCCACAGTGGCTCCACAGAGGTGAGTGTGGCCGTGACCCAGATGGTACCGGGATGCCGTGAGA
 GGGGATCGCTCATGATGCCAGCTGAGCGCCGCTGCCCTGAGCTCGTGTGGATGTGCTGGAGGGCCGGGCC
 CAGCACCCCTGGAGTCCTATGTGCAGAAGCAGTGTCCAACCTGCCAGCAGCTGCCAGCTGCTGCCTGAT
 CTGGAATCCCAGTGCCTGGGCCCTCCGAAGCCCTGGGAAAGATGCCGTGTAACCTCTGGCTGGGGAG
 GCGGCTGCAGTGACTCTTGACAAAGGACACTATGAGAACCTCTACTGCGTGGTCTCAGGAGAGAACGATTT
 CTGTTCCATCCGCCAGCGACCGGCCCTCATCCCTATGAGCTGTACACGCCGAAACCTACAGCTAACTGAA
 GAGGGCACCTTAAGGTGGTGGATGAAGAGGCCATGGAGAAGGCAGAGGTGTCCAGGACCTGCCTGTCACGGTT
 CGTGCCTGCAGGCCATGCCAACCCCTAAGGACCTAGTGACCCCTGACTGACTGACTCTGGCTG
 CCCACGGCTGCAGCCACAGGCTCCAGACACGACGGTCAAGAACAGCAGTAGCCCTGTCGGAACCAGAGCTT
 CACTTCAGGATCCACAGGCAGCTCAAGAACATGTCATGGAACGACTGTTGACCGAGCTGGTGCACGGAGAT
 GACCCCTGTTGTCAGTACTGTTGATGCGGGACTCTGCGGGCTGGGAGTCCGGCGAGAGCTTCTCACTG
 AGCCCTCAGGGTGAGGGCGCTGGAAAGTTGAATTGCGCTGCAGACTGGCTGACCGTGGCAGTGCTCGTC
 AGCAATGGCGTTCTGGTGGCCCGGGAGCTCTGCTTGACGTTCAACTGGAGGAGACAGGAGAACAGAACG
 TCAGAGCACAGAGTTCAGCTTGTTCTGGTCTGTGAGGGTCCGCAGGAGGCCTGTGGGACTGGCACC
 TTCCGCTTCACTGCCAACGCCGCTGGAGCAGGAGCTGAGTATTGCGCTGCAGGATGCCCGAGGAGCAACTA
 AAGGCCTGAGTGCCCTGCCCTGGTCAAGTGGTGAGGCTTGTCTCCCCACGTCAGGAGCCCTGATG
 AGAGTGGAGCTGAAAAAAGAACGAGCAGGACTGAGGGAGCTGGCGTGCAGCTGGCTTGGGCCCTGTGAGAGGAG
 CAGGCCTTCTGAGCAGGAGGAAGCAGGTGGTGGCCGCGGCCCTGAGGCAGGCCCTGCAGCTGGATGGAGACCTG
 CAGGAGGATGAGATCCCAGTGGTAGCTATTATGCCACTGGTGTTGGATCCGGCAATGACTCCCTGTATGGG
 CAGCTGGCTGGCCTGAAGGAGCTGGCCTTGGATTGCGTCTCCTACATCACCGGGCCTCGGGCTCACCTGG
 GCCTTGGCCAACCTTATGAGGACCCAGAGTGGTCTCAGAAGGACCTGGCAGGGCCACTGAGTTGCTGAAGACC
 CAGGTGACCAAGAACAGCTGGTGTGCTGGCCCCAGCCAGCTGCAGCGTACCGGAGCTGGCAGCGT
 GCCCGCTTGGCTACCAAGCTGCTCACCAACCTGTGGCCCTCATCAACGAGGCGCTGTCATGAGGCC
 CATGATCACAGCTCAGATCACGGAGGCCCTGAGCTGGCCAGAACCTCTGCCATCTACTGTCCTC
 AACACCAAAGGGCAGAGCCTGACCACTTTGAATTGGGAGTGGTGCAGTTCTCCCTACGAGGTCGGCTTC
 CCAAGTACGGGGCCTCATCCCTGAGCTTGGCTCCAGTTATGGGAGCTGAGCTGATGAAGAGGCTT
 CCTGAGTCCCGCATCTGCTCTAGAAGGTATCTGGAGCAACCTGTATGAGCCAAACCTCCAGGACAGCTTATAC
 TGGGCTCAGAGCCCAGCCAGTTCTGGGACCGCTGGGTCAAGGAACCAGGCCAACCTGGACAAGGAGCAGGTCCCC
 CTTCTGAAGATAGAAGAACCAACCTCAACAGCCGGCAGRATAGCTGAGTTTCACCGATCTCTGACGTGGCGT
 CCACTGGCCAGGCCACACATAATTCTGCGTGGCTCCATTCCACAAAGACTACTTCAGCATCCCACTTC
 TCCACATGGAAAGCTACCACTCTGGATGGCTCCCAACCAGCTGACACCCCTGGAGGCCACCTGTGCCTGCTG
 GATGTTGGCTACCTCATCAATACCAGCTGCCCTGCCCTGCAAGCCCACCTGGGACGTGGACCTCATCCTGTCA
 TTGGACTACAACCTCCACGGAGCCTCAGCAGTGCAGCTCTGGCCGGTCTGCCAGGAGCAGGGATCCCG
 TTCCCACCCATCTGCCAGGCCAGGGCAAGAGCAGCTCCAGCCTGGAGTGCACACCTCTCCGACCCACCTGC
 CCCGGAGCCCCCTGCCAGCTGGGAGGTGAACCTGTCTCATCGGACTCTCCCTACCAACTACAGAACGGTG
 CGGACACCCAGGAGGAGGCCAGCTGGGAGGTGAACCTGTCTCATCGGACTCTCCCTACCAACTACAGAACGGTG
 ACCTACAGCCAGGAGGAGCAGTGGACAAGCTGCTGCACCTGACACATTACAATGTCAGCAACACAGGAGCAGCTG
 CTGGAGGCTCTGCCAGGCAGTGCAGCGGAGGCCAGCGCAGGCCAC**TGATGGCCGGGGCCCTGCCACCC**
 CTAACCTCATCATTCCCTGGCTGCTGAGTTGCAAGGTGGAACTGTCATCACGAGTGCCTCAGCAGTTGCA
 TCAGGTGGCACKGCCCAGGGTCCAGGGTGGAGGCTCCCTGCGCCTCAGCAGTTGCAAGTGGGTA
 GGAGGCCAAGCCCATTGTGAATCACCAAAACCCCCCGGCCCTGCGCTGTTCCCTCTGCGTACCTTGAG
 TAGTTGGAGCACTGATACATCACAGACTCATACAAAAAAAAAAAAAA

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FIGURE 76

MAEAALEAVRSELREFPAAARELCVPLAVPYLDKPPPLHFYRDWVCPNRPCIIRNALQHWPALQKWSLPYFRAT
VGSTEVSVAUTPDGYADAVRGDRFMMPAERRLPLSFVLDVLEGRAQHPGVLYVQKQCSNLPSELPQLLPDLESHV
PWASEALGKMPDAVNFWLGEAAAVTSLHKDHENLYCVVSGEKHFLFHPPSDRPFIPYELYTPATYQLTEEGTFK
VVDEEAMEKAEVSRCLLTDRVRLQAHRLPSKDLVTPSDCYVTLWLPTACSHRLQTRTVKNSSSPVWNQSFHFRIH
RQLKNVMELKVFQDQLVTGDDPVLSVLFDAAGTLRAGEFRRESFSLSPQGEGRLEVEFRLQSLADRGEWLVSNGVL
VARELSCLHVQLEETGDQKSSEHRVQLVPGSCEGPQEASVGTGTFRFHCACWEQELSIRLQDAEEQLKAPLS
ALPSGQVVRLVFPTSQEPLMVRVELKKEAGLRELAVRLGFGPCAEEQAFLSRRKQVVAALRQALQLDGDLQEDEI
PVVAIMATGGGIRAMTSLYGQLAGLKELGLLDCVSYITGASGSTWALANLYEDPEWSQKDLAGPTELLKTQVTKN
KLGVLAPSQLQRYRQELAERARLGYPSCFTNLWALINEALLHDEPHDKLSDQREALSHGQNPLPIYCALNTKGQ
SLTTFEFGEWCEFSPYEVGFPKYGAFIPSEFGSEFFMGQLMKRLPESRICFLEGIWSNLYAANLQDSLYWASEP
SQFWDRWVRNQANLDKEQVPLLKIEEPPSTAGRIAEFFTDLLTWRPLAQATHNFLRGLHFHKDYFQHPHFSTWKA
TTLDGLPNQLTPSEPHLCLLDVGYLINTSCLPLLQPTRDVDLILSLDYNLHGAFQQLQOLLGRFCQEQQGIPFPPIS
PSPEEQLQPRECHTFSDPTCPGAPAVLHFPLVSDSFREYSAPGVRRTEEAAAGEVNLSDDSPYHYTKVTYSQE
DVDKLLHLTHYNVCNNQEQLLEALRQAVQRRRQRRPH

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FIGURE 77A

CCAGACAGCCTTGTATGGGAAGAGATGGGAAGGGTGAGGTGCCACATCCTTATGGGCACCGGAAGTTCATCACTAT
 GTCTGATGGAGCCACTTCTACATTGACCTCTTCGAGCCCTGGCTGAGCACTGTGTTGGAGATGATATCACCAT
 GGTCACTGCCCTGGAATTGCCACACAATTCAAAAGTTGGATCTGAAGTTGGAGAAAGATATTCCAACCTAAGT
 GGGTACTATTTGAAACCAGATTTAATTAAATGCCATATTGACTGCTATTTGAGTCTGTTGGATAGGTGTTCCAAAGTG
 TGTCTTCAGTGAAGAACGCAACTCTAGGTTCAAGTACTCCCTTCTCGATCCTGTGGACTTGAATATCCA
 AAAACCCCTGCACTTGAACAATCAGCTGTGCTATCTGGAACTAAACAGAACTATGAGTAAATTGCCCTGGATAC
 TTTAAAAAGATATTTCCTCCTTCATCTCCTTGACTCCAGGACAGACTGGAAATATAAGTAGTGGGTCTGCATG
 GATGTTTCAGGGATCAAAGGAGCCACCTGGCGCCTGAGTGCCAACCTCAGGGCCACAGGTGGGTGGTTGG
 GCACGGGTCCAAGTGACTGTGACGGGACCCCTGGCATGGGCCAGGTCTGTAACCTGAAGAAGTTGTTCTGA
 CAATCACCAAATCATCGAATGACATCAAAGCAGCCCTATCTCAGAGACCGAGATTCTGTGGTCTCAACTTC
 GCTTGGTATAATTCTGGCACTCACCAGCCTATCATTGACTTTCCCCCAGTGTATTATTCTCTAATAG
 GTTCTTTCACGTTCTTACAGACTGGCACTTACCCCTCAATTGGAAGTTAGCCCTCTCCTCTGT
 TACTTTCCCTCACCCAACCTACAGCTGTGATCTAGAACATTCTAGTCATATTCTGCTACTACTACCTTCATT
 TATCAAGACTTTATGAGAATAGGTAAACCAAGAATAACTCCTAGGACTGAATCACCACCCAGAAGAGCGA
 GAGGCTCTTCATATGCCCTGAGGCCACACCCCTAACCTGTTGACAAAATAGTGGCTGCCACACAACCG
 TCCATTCAAGAAATTCAAGGAAGGAGAAAAGACAGCCCTGTTGTCACACAAACGGGTGGGGAGGGTGGAGCCTGG
 TCTGCACGGCAGTCTGGTGGCCCTGTTGAGGACAGGCAGGGCTGGCAGCATAGCCTTGTGCCCCATGTACCG
 GAATTGCTCCCCCAGGACTGTGGGAGCCAGTGTCCCAGCTGAAATCTTTAGTGTGTGGCTCTGAATGGCACT
 CACATTCCATTGGCTCACATGAAACTAACAGTGAAGCCCTTGTCAAGCTCAGGCTCTAGGCATGAAATGA
 GAATGTGACTGTGGCTGTCTACAGGAAAATTCTGTTGTCCTGAATGAGAGCACAGAGGCATTGAATTACA
 GAGCTGCAAACCTGCCTGATAAAATGAGGGAGTGGCAGTTATAGATAGGTCACTTTTCTCCTCAGGTGT
 CCTTGCCCTTCTCCCAAAGTCATTCTGATGAGTATATGAATCCCCCTTGTCTAGTAAGGTTCTATTG
 GGCTAAAACAAGGCTGAATTAAAGAGTATTGAATATAATTAGAATCAAATTGAGGCTATAATTGCATCA
 ATCTGGACAATTCCATTGAGGAATAATATGTTAAAACCAATGGGGAGACACCCACATCTCCTGTAGCAC
 TCCGTGTCTCATAAGCAATTGAAGACACTTACAAGTAACTGATTCCAGTCAAATTAGGATTAACTGACTCAAA
 AATGGTGTCAAGTTCTTAATGTTTATGTTAGAAGTGAAGTTAACAGACTGAAGAAAATGTTATCTTTC
 CTGCTGTGAGTTACACAAATGATTCCAGAGCAGAATGAAAGCAGAAAGCTGTTGTTACAATATTCTTAAAC
 TCTCTGCAGCATTACACTTACTGGAACCTTATGATTCAACCGTAAGAGTGGAAATACCTGAGTTCGTGTCC
 TAATGGTCTCTAATTCAATTGGATGTCAGGCAACATCACCTCACCTCTGAGCCTGTTCCCTCTTAGACCA
 TCTCTAAGACCACCTCATCTATTACACATCATTGCTGAACATTGCTGAACATCTCGTGAACCTGGCCTCTC
 CAGCCCTGCAAGGGAAACAGCTGTGCAAGGCTCAAGGCTCACGCTGAGGGACTTGGAGGGAGGGGCTTCT
 GCATTAAGCTTCTGGTGAAGACCCCTGATCTTGTCAAAGCCCTGTTGACTGGCTCTCTCAGAGTC
 CCCGGTGTATCGTAAGACCCCTGCTGTTGGAGGGTGGCTTGTGACTGTGGCAGCTGTCGGCCGCTGGAAATGA
 GGAGCCTATCTCCATTCCAGTGTGACTCAGGCAGAGCATTGAGAATTCCCAGGGCAGAAATCTCTGCTCA
 GGCTTTCATTCTAAACTACAGTCTTCATTAAAGCTGAACATTCTGGTAGCTGAGCTTATATGCCCGCATTCTG
 AATGAGAGCTCTTGTAACTGTGTGACTTGAGATCTAGTTGCCAGCTCCTGGAAACAATACATGTGTTCTT
 GTTGTGTTGCTCAGCAAGCAGATGCTGAGATGTAAGAAGCTTCTTCTGTTGAGCTTGTGACTTA
 GAGCTGAAGTAAAGATCACTGAAACATCACGTCAAGTGAAGTCACTCATAGGTCTTGTGCTTCTAGGAGGACA
 GGAGAGTCATTAAAGAACATTCACTGTAGCATTCTATCACAAATATCATGGAAATTGTTCTTGTGCTTCT
 GCCTTAACCTGCCTCTAGAGAATCCCTGGTATTACAACGATATTGCGGCATTAGAATTCAACTCTCTGCTGTG
 GAAGTTGAAGCGAAGCTGCAAGCAAAACCAGAGAATTCCCTCAAGTGGCCTGTAGGCTCTTGTTATCTTATGCC
 CCCACCCCTCCCTCAACAATATGAGTGTGATCCAGAACTGGCCAAACACCTCAGCTCTGGTCCCTTTGCCCCTC
 TTGGCCTTACTCTGTTGTCAAAGCCACTTGGATTGCTGGATGTCGAACAGCCATGAAAAGTAGCCTGCCT
 GTGGCATTAGAGGCCAAGCAATTGACAGAAAGGGTTCTTCTACCTCTGTTATCTAAGCAGAGGGAAAGTAAACT
 TCTCACCGCCCCCACCCTCACTGCCCGATTACACTAGAATTGCTTGCCTAAATTGAGTTGAAGCTAAGG
 AAGGGAAATCTGGCCCTGCTGGAGAGGGAACTGGAATGCCACACAAGGCAAGGCCGCTGCTCCCTCC
 CTGCTGCTGCTGCCCTGGAACGCTGCAAGCCCAGGCTCCCTCCACAGTGGCCCTTGGAAAGCAGGCCAGAGTAG
 ACAGCTGCTCTTGGAAAGAGTCAGTCCCTGTGTTCTGAACCTGTTTCTAGCATGTATGTGGTAGAGC

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FIGURE 77B

TTTCATGCATCTAGTAATAATAAGCTGAAATTAGTTTTTTTAATTCTCCAATTAAAACCTTTAATTAAA
AAGTAAATTAAATGTCGAAAATGCAAACCTGGGAGGGCAGAAAGATCACACACAAGGCTGTCACTCATACTT
GCAGGATTGCACAGCAGCCGGCAGAGGCCTCCACTTCCCAGATGGGCGGGCAGCAGAGACGCACCTC
ACTTCCTAGACAGTGCAGCACCAGGCACAGGCACACCTCAGTGGGCGGCCAGGCAAGCGCTC
CTCACTCCCCAGATGGGCGGCTCCCGGAAGCGGGCTCCCTACTTCCCAGACAGGGTGGCCAGGCAGAGGT
GCTCCTCACTTCCCAGAACAAATTCTTATGAATTGATAAAAGGACTGAAGTGCAACTGAAAGCTGCTAGTGATGA
TCTGGTAATATAACAATTGTCAGTAGCCAGTTGTTTIAATTGTGTTTCTAACCATAAAGAGATCATTAAGGC
AAAGCCTGTATGACGCTGTACACACACAAAAAAATGGTACCGCAGGCCACTACCAATGAAATGGTAGGTAAA
CAAATCTCTGGTCAAGAGAAAAAAAGAAATAGCACTCTGCATGCTTGCTACAAGATGAATTCCCTAG
AAAGAATCCAATGAAGGCCGGCATAAGTGGCTCACT

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FIGURE 78

QTALYGMGRVRSPHPYGHRKFITMSDGATSTFDLFEPLAEHCVGDDITMVICPGIATQFKSWI

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FIGURE 79

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FIGURE 80A

CTGCCACCACATCTTGTCCCTGGCAAAGTGGGTTTGCAGTGGCTAGACCTAGAAAAGAATCGTACGGGCA
 GGAAACCATTACACCACCTGGCTGTGCTCTCCGGCTCCGCCACCCCCGCCCTGCCCTGCCCTCCG
 TCCGGTGCACATTAAGATCAAAGTCATGACTGACTCCAAGTATTACAACCAATAAAAAGGAGAAATATT
 GAACTAAAGCTGAACCAACATGAAAAGAAAAGAGAAGGAGGCTGTGAAGAAAGTGATTGCTGCTATG
 ACCGTGGGAAGGATGTTAGTCCTCTTCCAGACGTAGTGAACGTATGCAGACTGACAATCTGGAAC
 AAGCTTGTATCTACTTGATGAACATGCCAAGAGTCAGCCAGACATGCCATATGGCTGAAACAGCTT
 GTGAAGGACTGTGAAGATCCTAACCTTGATTGAGCCTGGCAGTCAGAACATGGGTGCATCCGGTAGAC
 AAAATTACAGAATATCTGTGAGCCGCTCCGCAAGTGCTGAAGGATGAGGATCCCTATGTCGGAAA
 GCAGTCTCGTGGCAAAACTCCATGATATCAATGCCAATGGTGAAGATCAGGGATTCTGGATTCTACGG
 GATCTCATAGCAGATTCAAATCCAATGGTGGCTAATGCCGTAGCCGATTATCTGAAATCAGTGAGTCTCAC
 CCAAACAGCAACTTACTTGATCTGAACCCACAGAACATTAAAGCTGCTGACAGCCCTGAATGAATGCACTGAA
 TGGGCCAGATTTCATCCTGACTGCCGTCTAATTACAACCTAAAGATGATCGGGAGGCTCAGAGCATCTG
 GAGCGGTAACCTCCCGCTATCCATGCCACTCAGCAGTGGTCTTCAGCGTAAAGCTTAATGAAAGTT
 CTAGAATTGTTACCTAACGGATTCTGACTACTACAATATGCTGCTGAAGAAGTTAGCCCTCCACTGTC
 CTGCTGGGAGCCAGAAGTGCAGTATGCGCCCTGAGGAACATCAACTTAATTGTCAGAAAAGGCTGAAATC
 TTGAAGCAGGAAATCAAAGTCTTGTGAAGTACAATGATCCCCTATGTTAAACTAGAGAAGTTGGACATC
 ATGATTGTTGGCATCTCAAGCAACATTGCTCAGGTTCTGGCAGAACTGAAAGAATATGCTACAGAGGTGG
 GTGACTTGTGAAAGCTGTGCGGCCATTGGACGGTGTGCCATCAAGGTGGAGCAATCTGAGAGCGCTG
 GTAAGCACATTGCTGATCTAACAGACCAAAAGTAATTATGTTGCTCAAGAAGCAATTGTTGTCATCAGGG
 ATCTTCCGCAAATACCCAAACAAGTATGAAAGTATCATGCCACTCTGTTGAGAAGCTAGACTCGCTGG
 CCAGATGCTCGAGCAGCTATGATTGGATTGTTGAGAATATGCTGAAAGAATTGACAATGAGATGAGTT
 GAAAGCTCCTGGAGGGTTTACGATGAAAGCACCCAGGTGCAGCTCACTCTGCTTACTGCCATAGTGAAGCT
 TTTCTCAAGAAACCATCAGAAACACAGGAGCTAGTCCAGCAGGTCTGAGTTGGCAACACAGGATTCT
 CCTGACCTTCGAGACCAGGGCTATATTATTGGCCCTCTCAACTGACCCCTTACAGCTAAAGAAGTAG
 TTGCTGAGAAGCCACTGATCTGAGGAGACGGACCTTATTGAGCCAACCTGCTGGATGAGCTAATCTGCC
 ATTGGTTCTTGGCCTCTGTTGATCTAACGCTCCAATGCTTGTGAGAAGTCATGAAATTGTCATCGTAA
 CACTTGCCATTACATGGGAGCACTGATGCAGGTGACAGCCCTGTTGCACTACCACTGCAACGAACCTGG
 CAGCCTCAGGTTATCCCCTCAAGGTGATCTTAGGGATCTTAAACCTTGACCTCGTCCCCAGTC
 GTGCCACAGGTGCTCCATGCAGATGGAGCAGTGGATCTCTAGGAGGAGACTAGATAAGTCTGGTGG
 TCCTTCATCCCATCATCGGTGCCTGCAACCTTGCCTTCACCTACACCTGCTGTCAGCAGTGGACTGA
 GACCTGTTGAACCTCCACAGGGATAGGCATGGCACCTGGGATATGTCCTAAGGCTGCTGGCTAC
 GCAGTAAAGGCTAAAGGCTGGAGATTCCGAAACATTACTCACCGCAAGGGCACATCTATATGAA
 TTCACCAATAAGCTGAGCACATGACAGATTGCAATTGCAACAAAGTAGCTTGGTGCATCCCC
 AGCACTCCTCTGGCCATCCATACACCAACTGATGCCAACCCAGAGCATTGATGTCCTCCCTGCC
 GGCCAGTCATGAAGATGAAACCTCTGAATAACCTCCAGGTGGCTGTGAAAACAATATGATGTCTT
 AGCTGCCCTCATCCACTCAATGTGCTTTGTTGAGAAGATGGCAAAATGGAGGCCAGGTCTCCT
 AAGGATATTCCAAATGAAACTTCAGTTGAGGATGTCATTAAATGCTGACACTGTTCCAGC
 AAGTTGCAAACAAACATGTTATACTATTGCAAGAGGAATGTTGAGAAGGGCAGGACATGCTG
 AACCTGACTAATGGCATTGGATTGGCCGAACCTACGTTACGAGCATTGAGCTAAGTCT
 AAGTGTAGAGCTCTGAAGTCTCTCAATACATCTCAGGTCTACGACAGCATTGAAA
 ACTTAACAAGACTGG
 TCCAGTACCCCTCAACCAGTGTGATCGGTGCAAGTCAGAACACTCTTA
 ACTGGAAGAAATTGTTATTGCTGCTGTAACATTAGGGCACAACCTGT
 GAATCTGAACACACTGAGGCCACCTAGCAAGGTAGTA
 ACTGTCATTGCTGCTAACATTAGGGCACAACCTGT
 TGGATAGTTTAGCTCCTGTGAACATTGTAACCACTGCTCAGTCAC
 CCTCCACCTCTGCCCCACCTGCTGCTGCTG
 CTATCTGCTTACTTGTGGCTTCTCCATGCTGCAATGGCTGG
 TTTCTACACCCCTTTGAGTGTAG
 TTTGGTATTGTAATTGAGAGCTCATTC
 AAAAGCAGAAAAGACAACAAATATTAAAGCAAGGAAAAGTGTAA
 CTGAAACACTGCAC
 TTTACTGTTACTGTTACTTTGACATATGAGAAATCAAGGGATTAG
 TGTGCAACCAGTAGAAGG
 CATTGAAATGACTGTCATTAACCACACAGTC
 CCTGGAGGCAGAGATGCA
 GAGTTACCTACCC
 TAGCTAGCTTGTGCTA
 ACATTAGGGCACA
 CCTGT
 CTCTTACCTGTAGTAGC
 CCTTATCCCTGG
 CATTGGATTTCAG
 TTTGCTTTCT
 TTTTCC
 CCAA
 ACT

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FIGURE 80B

CCTTTCTGGCCAAGCCTCATGCTCCCCCTTCCATATTATAATCTCATTGATTGCTCTGCAGTTGGAA
CGGTGATCTTCTGAATGATGATTTCAGTGTGCAAAAACATATAGAGCCTGTCAAGCACAAAGCTGACAGAAAGTTAT
ACCTTACTCCTTCTTCCCTGAACAAACCTGTAATCCACTAATTAGGAATTGAGTAGAGATGGGAAC
AAGAACCCAGATGCTGCCCCCTACCCCCCTCCTGTATTCTCAGGTCCAGTCAAATCTAAAATTCTACTTT
AGAGTTGAAACAGAGTAATAACTTATCTAACCCCTTTCTACAAAGGAGAAAGATAAAAGGCACAAAGGTTAC
CGCCAAGGCCGTCAGCTGTAGTGGAAAGCCGAGACCGAGTCTCTAAGTCCCCTCAGTGTGGTTTCACC
ACAGGACTGTCTTGTCTTCCCCTAATGCCCTCTCCTGCCTTTCTGTGCCTAGTTTGGCTCTCACAT
ATTCCATATTGATTGACGCTCTGTATATTGGCATCAGTGGCAGCTGAATATCTTGAATTACTCGAAGGTA
AAGCCAGATGCCAGAATGAAGGTGTAGCCAGTGTTCATATGCCCTGGAGCCCCACTTATTGAGGCCAGCAG
AATAGGTGCAGAGATGAAGTGAGCTTAGAGATGTGCAAATGCTCTTATCCCTCAGCTCTGATCTGCTCTT
TCTCATGATACTTAGTCTGCAGGGCATATTAAGATCATCCAGAGGTCAGGCAGTTCTGTATCTGAAAA
GACTGGGGATATGAAATCTCCCCTACCCACTTAATGCGTTGGATATGATTTCAAAGAATGCTCATGCC
CAAAATACCAGCCTGTTAGCAGTGTACACTGTTGATCTGCCGGCACTTGTGCATTGCCCTGGCACCCAAATAT
TCAGGGTCCATGACTAAGACTGGCTTCTCAGATGCCCTGCTTAAATCAGGGGCACTTCAGGCTCCACAGCGTC
ATGTTGGACTGAGACCTAACACTGACTCAGAGGAGGAATCGTGGAAAACAAGAGCAAACACTACCCACACCC
CTATTCATGTCTGAAATAACCTGTTCATACCACTGCAAAGCTTGTGGGAGCGGTCCACAAAGCACTTCT
TTAACCTTGAGAATCTCAAGAGAAAATTTGGGAAGGAGGGAGGAATATGTCCTTGACACACCACCC
GAAGCACATGGCAGTAGGAAACAGCATAGGATTGTATGTGGAGGTGGATAGGTGGTGTGGAGCGGAAA
AGCAGGTTGGTAAAGTCCCTCTGGGACTTATTCTGGAGTCAGTGGATACAAGTAGTGTGCAGAAGGTTCACAC
TGCAAATAGTGTCTCATCTCAAAGCAAACATCATTCCAGAAGGAAAAGTGTGTCAAGGGCAAGCAGACAACACA
ATTCCTATCAGAATATGTCCTCAACCCCCGAAACAAGGCTCTCAGCCTCCCCACCAGTGTGGATAACAG
CTCCTATTCTCAGCTGACCTGACTGAGCCAACCCATGAACCTTCACTCCTGGGAAGCCACCTCCATCACAC
CCCTGAGCAGAGTTAGGGAGGAATTCTACTTCCATAAAAGGACCTCTGAGAGGGCAAACCTGTTGCCTCCA
CCACGGCTCCCTTGGCTATTCCAAGCTGGCAAATTGGGAAGTGGATGGAGGTGGCCCTGCATCCCC
CTCCTCTGCTGAGTGTGTCTTGTAATGTCAGCTGGCATACAAAGAGCAGGAGAAGCAAACACCCAGAACT
CTTTGCTGGTCAAGAGATTCCCTGAGTGTCTGTCTCACCCAGCCTGCTCTGTGTGTGTTGTGAAGCTTGAG
ACTCTGGAAAGAAATGGGGAGGGGGGGCAGGGAAATGTTGCCCTAAGAATGCTCTCATTCCTGTCTTATT
GGTCCTGTTTCTGGAGGGTGGGGGGAGCTTGACCTTGTCTCGTCAATAACTCACATTACA
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FIGURE 81

MTDSKYFTTNKKGEIFELKAEVNNEKKEKRKEAVKKVIAAMTVGKDVSILFPDVNCMQTDNLELKKLVLYLMN
YAKSQPDMAIMAVNSFVKDCEDPNPLIRALAVRTMGCIRVDKITEYLCEPLRKCLKDEDPYVRKTAACVAKLHD
INAQMVEDQGFLDSSLRDLIADSNPVVANAVAALSEISESHPNSNLLDLPQNINKLLTALNECTEWGQIFILD
LSNYPKDDREAQSICERVTPLSHANSAVVLSAVKVLMKFLELLPKDSDYYNMLLKKLAPPLVTLLS
GEPEVQY
VALRNINLIVQKRPEILKQEIKVFFVKYNDPIYVKEKLDIMIRLASQANIAQVLAELKEYATEVDVDFVRKAVR
AIGRCAIKVEQSAERCVSTLLDLIQTKVNYVVQEAIIVVIRDIFRKYPNKYESIIATLCENLDSLDEPDARAAMIW
IVGEYAERIDNADELLESFLEGFHDESTQVQLTLLTAIVKLFLKKPSETQELVQQVLSLATQDSDNPDLRDRGYI
YWRLLSTDPTAKEVVLSEKPLISEETDLIEPTLLDELICHIGSLASVYHKPPNAFVEGSHGIHRKHLPIHHGST
DAGDSPVGTTTATNLEQPQVIPSQGDLLGDLLNLDLGPPVNPQVSSMQMGAVDILGGGLDSLVGQSFIPSSVPA
TFAPSPTPAVVSGLNDLFELSTGIGMAPGGYVAPKAVWLPAVKAKGLEISGTFTHRQGHYMEMNFTNKALQHM
TDFAIQFNKNSFGVIPSTPLAIHTPLMPNQSIDVSLPLNTLGPVMKMEPLNNLQAVKNNIDVFYFSCLIPLNVL
FVEDGKMERQVFLATWDIPNENELOFQIKECHLNADTVSSKLQNNNVYTIAKRNVEGQDMLYQSLKLTNGIWL
AELRIQPGNPNTLSLKCRapeVSQYIYQVYDSILKN

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FIGURE 82

GGCACGAGGGCGCGGAGCGGGAGCGGGCGCAGCTAGCGGGTGGCCGGAGCGGGAGGTGCAGCTGGCT
TCCCCCGGCACCCCTCCCCCTGGCGCCAGCCCCACCCCTCCGCCGGCCGGCCGACCCCGCTACTATCCCC
TGCGGCGCGAGCCCGGGCGGCTCCAAGCGCCCCCAGCAGACCCCCATCATGGCAGCCAGAGCTCCAAGGCTC
CCCAGGGCGACGTGACCGCCGAGGAGGCAGCAGGCCTTCCCCCGCGAAGGCCAACGCCAGGAGAATGCCACG
TGAAAAGCAATGGAGACTTATCCCCAAGGGTGAAGGGAGTCGCCCCCTGTGAACGGAACAGATGAGGCAGCCG
GGGCCACTGGCGATGCCATCGAGCCAGCACCCCTAGCCAGGGTGTGAGGCCAACGGGGAGGTCCCCCCCAAGG
AGACCCCCAAGAAGAAGAAGAAATTCTCTTCAAGAACGCCCTCAAAATTGAGCGGCCGTCTTCAAGAGAAATC
GGAAGGAGGGTGGGGGTGATTCTCTGCCCTCACCCACAGAGGAAGAGCAGGAGCAGGGGAGATCGGTGCCT
GCAGCGACGGGCAGTGCAGCCTCAGAAGAAGAGGCAGGGCCCCAGGCTACAGAGCCATCCACTCCCTGGGGCGAGA
CAGAGGCTAGTGCAGCCTCAGAAGAAGAGGCAGGGCCCCAGGCTACAGAGCCATCCACTCCCTGGGGCGAGA
GTGGCCCTACACCAGCCAGCGCTGAGCAGAATGAGTAGCTAGGTAGGGCAGGTGGGTGATCTAAGCTGCAA
AACTGTGCTGCTTGTGAGGTCACTGCCCTGGACCTGGTGCCTGGCTGCCAGAAAGGAAGGGG
CTATTGCCCTCCTCCCAGCCACGTTCCCTTCTCCTCTCCCTCTGGATTCTCCCATCAGCCATCTGGTCTC
CTCTTAAGGCCAGTTGAAGATGGTCCCTTACAGCTTCCAAAGTTAGGTTAGTGTGAAATGCTCTGTCCCTG
GCCCTACCTCCTCCCTGCCCCACCCCTGCATAAGGCAGTTGGTTCTTCCCAATTCTTCAAGTAG
GTTTGTTTACCTACTCCCCAAATCCCTGAGCCAGAAGTGGGTGCTTAACTCCAAACCTTGAGTGTCCAGC
CTTCCCTGTTGTTTACTCTTGTGCTGTGCTAGTGGCACCTGGCTGGGAGGACACTGCCCGTCTAGG
TTTTATAAATGTCTACTCAAGTTAACCTCCAGCCTGTGAATCAACTGTGCTCTTTTGACTTGGTAAGC
AAGTATTAGGCTTGGGTGGGGGAGGTCTGTAATGTGAAACAACCTCTGTCTTTCTCCACTGTTGTA
AATAACTTTAATGGCAAACCCCAGATTGTACTTTTTCTAACTGCTAAAACCATTCTCTCCACCT
GGTTTACTGTAACATTGGAAAAGGAATAATGTCGCCCTTTAaaaaaaaaaaaaaaaaaaaaaaa

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FIGURE 83

MGSQSSKAPRGDVTAEEAAGASPAKANGQENGHVKSNGDLSPKGEGESPPVNGTDEAAGATGDATEPAPPSQGAE
AKGEVPPKETPKKKKFSDKPKFLSGLSFKRNRKEGGDSSASSPTEEEQEQGEIGACSDGTAQEGKAAATPE
SQEPQAKGAEASAASEEEAGPQATEPSTPSGPESGPTPASAEQNE

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FIGURE 84

GCGGAGCGTGTGAGCAGTACTGCGGCCTCCTCTCCCTACCTCGCTCGCGGCCTACCTTACCCGCCG
 CCTGCTCGCGACCAGCGGGATCCTCCCCAGCGCAAGTCCACGAAGAAAGCAACGAATGAAAATTATGAAGA
 CAACGAGAAGTCAGACTCCTCGGGTCGCGCTCCAGCTGCTCGCTCGCCACTCTGTGAACCTCGGGGA
 GAGATCTGAGTCAAGATTAAGACCTAACCCACCAACCTGCCCTGTTGGACACCCCCCGGGCCGCCGTGTCT
 GTCCCCCTCTCATGCCCTCTCCAGAAAGCTCCGGTCTGGACCAGCTAGAGTCTGAGAAAGAGGAGAGGCG
 CGAACGCCACTCCAAAAGAGAAGGGTAAAGAGGGCAACCTAACGATACGCTTGACTTCTGTGGCTGGGAAC
 ACCTCCACCAATGACCACCTCAGCAAGTCCCACCTAACATAAGGCATCAAGCAGGTGTACATGCCCTGCCCTCA
 GGGTGAGAAAGTCCAGGCCATGTATATCTGGATCGATGGTACTGGAGAAGGACTCGCCTGCAAGACCCGGACCC
 GGACAGTGAGGCCAAGTGTGGAGAGCTTGCCCTGAGTGGATTCTGATGGCTCCAGTACTTACAGTCTGAGGG
 TTCCAACAGTGACATGTATCTCGTGCCTGCTGCCATGTTGGGGACCCCTCCGTAAGGACCTAACAGCTGGT
 GTTATGTGAAGTTCAAGTACAATCGAAGGCCCTCAGAGACCAATTGAGGCACACCTGTAACGGATAATGGA
 CATGGTGAGCAACCAGCACCCCTGGTTGGCATGGAGCAGGAGTACCCCATGGGACAGATGGGCCACCC
 TGGTTGGCCTTCCAACGGCTTCCCAGGGCCCCAGGGTCCATATTACTGTGGTGTGGGAGCAGACAGGCCATGG
 CAGGGACATCGTGGAGGCCATTACCGGGCTGCTGTATGCTGGAGTCAGATTGGGACTAATGCCGAGGT
 CATGCCCTGCCAGTGGGAATTTCAGATTGGACCTGTGAAGGAATCAGCATGGGAGATCATCTGGTGGCC
 TTTCATCTTGCATCGTGTGTGAAGACTTTGGAGTGTAGCAACCTTGATCTTAAGCCATTCTGGGAACTG
 GAATGGTGCAGGCTGCCATACCAACTTCAGCACCAAGGCCATGCGGGAGGAGAATGGTCTGAAGTACATCGAGGA
 GGCCATTGAGAAACTAACGAGCCGACCAAGTACCCATCCGTGCCTATGATCCCAAGGGAGGCCTGGACAATGC
 CCGACGTCTAACTGGATTCCATGAAACCTCAACATCAACGACTTTCTGCTGGTAGCCAATCGTAGGCCAG
 CATA CGCATTCCCCGGACTGTTGCCAGGAGAAGAAGGGTACTTTGAAGATCGTGCCTCTGCCACTGCGA
 CCCCTTTCGGTGACAGAACCCCTCATCCGCACGTGCTTCTCAATGAAACGGCGATGAGCCCTCCAGTACAA
 AAATTAAGTGGACTAGACCTCAGCTGTTGAGGCCCTCCTAGTTCTCATCCCACCTCAACTCTCCCCCTCTCC
 CAGTTGTCCTGGATTGTAACTCAAAGGGTGAATATCAAGGTCGTTTTTCATTCCATGTGCCAGTTATCTTG
 CTTCTTGTGTTGGCTGGGATAGAGGGTCAAGTTATTAAATTCTTCACACCTACCCCTCTTTTCCCTATCA
 CTGAAGCTTTAGTGCATTAGTGGGGAGGAGGGTGGGGAGACATAACCAACTGCTCCATTAAATGGGTGCACC
 TGTCCAATAGCGTAGCTATCCGGACAGAGCACGTTGCAGAAGGGGACTCTCTCCAGGTAGCTGAAAGGGG
 AAGACCTGACGTACTCTGGTTAGGACTTGCCTCGTGGTGGAAACTTTCTAAAGTTATAACCAACT
 TTTCTATTAAAGTGGGAATTAGGAGAGAAGGTAGGGGTTGGGAATCAGAGAGAATGGCTTGGCTCTGCTTG
 TGGGACTAGCCTGGCTGGGACTAAATGCCCTGCTCTGAACACGAAGCTTAGTATAAAACTGATGGATATCCCTAC
 CTTGAAAGAAGAAAAGGTTCTACTGCTGGCCTGATTATCACACAAAGCAGAATAGTATTAAATTTAA
 ATGTAAGACAAAAAAACTATATGTATGGTTGGATTATGTGTGTTGCTAAAGGAAAAACATCCAGGT
 ACGGGGCACCAATTGAGACAATAGCGGATTAGAAATAAGCATCTCATTTGAGTAGAGAGCAAGGGAAAGT
 GGTTCTTAGATGGTACTGGGATTAGGCCCTCAAGACCCCTTGGTTCTGCCCTGCCACCCCTGGAGAAG
 GTGGGACTGGATTAGTTAACAGACGACACGTTACTAGCAGTCACTGATCTCGTGGCTTGGTTAAAGACA
 CACTTGTCCACATAGTTAGAGATAAGAGTTGGCTGTTCAACTTGAGCATGTTACTGACAGAGGGGTATTGGG
 GTTATTCTGGTAGGAATAGCATGTCATAAGCAGGCCCTTGTATTTAAATTAAAGCAAAATTATA
 GAAGTTAGTTAATCAAATTGTTAGGGTTCTAGGTAATTAAACAGAATTGCTTGTGTTGCTCAACTGTCT
 CCTACCTCTGCTCTGGAGGAGATGGGACAGGGCTGGAGTCACACTTGTAATTGTATCTGATGTCTTT
 GTTAAGACTGCTGAAGAATTATTCTTATAAAAGGAATAACCCACCTTATTCTCATTTCTCATC
 TACCATTTCTGGTTCTGTGGCTGAGGCCAGCTGTTCTTGCATGACAACCTTAATTG
 CATGTACAGTATGTTCAAAGTCAAATAACTCCTCATTGTAACAAACTGTTGTAACGCCCCAAAGCAGCACTTATA
 AATCAGCCTAACATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 85

MTTSASSHLNKGIKVQVYMSLPOGEKVQAMYIWIDGTGEGLRCKTRTLDSEPKCVEELPEWNFDGSSTLQSEGSNS
DMYLVPAAFRDPFRKDPNKLVLCEVFKNRRPAETNLRHTCKRIMDMVSNQHPWFGMEEQYTLMGTDGHPFGWP
SNGFPGPQGPYYCGVGADRAYGRDIVEAHYRACLYAGVKIAGTNAEVMPAQWEFQIGPCEGISMGDHLWVARFIL
HRVCEDFGVIATFDPKPIPGNWNGAGCHTNFSTKAMREENGLKYIEEAIKEKLSKRHQYHIRAYDPKGGLDNARRL
TGFHETSNINDFSAGVANRSASIRIPRTVGQEKKGYFEDRRPSANCDPFSVTEALIRTCLLNETGDEPFQYKN

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FIGURE 86

AGTATGTGTGGTTGGGAATTCATGTGGAGGTCAAGAGTGGAAAGCAGGTGTGAGAGGGTCCAGCAGAAGGAAACAT
GGCTGCCAAAGTGTGAGTCATTGCAAGTTGGCTGGCTTAGCTGTTGCAGGAGGCGTGGTAACCTCTGC
CTTATATAATGTGGATGCTGGCACAGAGCTGTCACTTTGACCGATTCCGTGGAGTGCAGGACATTGTGGTAGG
GGAAGGGACTCATTCTCATCCGTGGTACAGAAACCAATTATCTTGACTGCCGTTCTGACCACGTAATGT
GCCAGTCATCACTGGTAGCAAAGATTACAGAAATGTCACACTCACACTGCGCATCCTCTCCGGCTGCGCCAG
CCAGCTTCTCGCATCTCACCAAGCATCGGAGAGGACTATGATGAGCGTGTGCCGTCCATCACAACTGAGAT
CCTCAAGTCAGTGGTGGCTCGCTTGATGCTGGAGAACTAATCACCCAGAGAGAGCTGGTCTCCAGGCAGGTGAG
CGACGACCTTACAGAGCGAGCCACCTTGGCTCATCTGGATGACGTGTCCTTGACACATCTGACCTTCGG
GAAGGAGTTACAGAAGCGGTGGAAGC_{AA}ACAGGGCTCAGCAGGAAGCAGAGAGGGCCAGATTGTGGTGG
AAAGGCTGAGCAACAGAAAAAGCGGCCATCATCTGCTGAGGGCAGTCCAAGGCAGCTGAGCTGATTGCCAA
CTCACTGGCACTGCAAGGGATGGCTGATCGAGCTGCGCAAGCTGGAAGCTGCAAGGAGACATCGCGTACAGCT
CTCACGCTCTCGAACATCACCTACCTGCCAGCGGGCAGTCCGTGCTCCCTCAGCTGCCAGTGAGGGCCAC
CCTGCCTGCACCTCCGGCTGACTGGGCCACAGCCCCGATGATTCTAACACAGCCTCCCTGCTCCCACC
CCAGAAATCACTGTGAAATTCAATGATTGGCTAAAGTGAAGGAAATAAGTAAACACTTCAGATCTTAAT
TAGTCTATCAAATGAAACTCTTCATTCTCATCCATCTACTTTTATCCACCTCCCTACCAAAAATTGC
CAAGTGCCTATGCAAACCAGCTTAGTCCCAATTGGGGCCTGCTGGAGTTCCGGCCTGGCACCAGCATTGG
CAGCACGCAGGGCAGTATGTGATGGACTGGGAGCACAGGTGTGCCTAGATCCACGTGTGGCCTCGC
CTGTCACTGATGGAAGGTTGCGGATGAGGGCATGTGCGCTGAAGTGAAGGAGGGCAGGGCTCCGTCTCCAGCG
GTTCCGTGCAAGATGCTGCAAGAGAGGTGCCGGGAGGGCAGAGAGGAAGTGGTCTGTCGTTACCATAGT
CTGATTCTCTTAATGTTGACCAGCGAACAGGTGTGAACTGGGCACAGATTGAAGAATCTGCCCTG
TTGAGGTGGTGGCCTGACTGTTGCCCTCAGGGCTCTAAACTGGATGGACTTGTATAGTGAAGAGAGGAGGC
CTGGACCGAGATGTGAGTCCTGTTGAAGACTTCCCTCTACCCCCCAGCTGGTCCCTCTCAGATAACCAAGTGG
ATTCCAACTTGAAGGATTGCATCCTGCTGGGCTGAACATGCCGCCAAAGACGTGTCCGACCTACGTTCTGG
CCCCCTCGTTCAAGAGACTGCCCTCTCACGGGCTCATGCCCTGCACTGGGAAGGAAACAAATGTGTATAACTGCT
GTCAATAATGACACCCAGACCTTCC

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FIGURE 87

MAAKVFESIGKFGLALAVAGGVVNSALYNVDAGHRAVIFDRFRGVQDIVVGEETHFLIPWVQKPIIFDCRSRPRN
VPVITGSKDLQNVNITLRILFRPVASQLPRIFTSIGEDYDERVLPSITTEILKSVVARFDAGELITQRELVSQV
SDDLTERAATFGLIILDDVSLTHLTFGKEFTEAVEAKQVAQQEAERARFVVEKAEQQKAAIIISAEGDSKAAELIA
NSLATAGDGLIELRKLEAAEDIAYQLSRSRNITYLPAGQSVLQLPQ

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FIGURE 88

GGCACGAGGGGCCGGGGGCGCAGCTAGAGAGCCCCGGAGGCCGCGGGAGAGGAACGCGCAGCCAGCCTGGG
AAGCCCAGGCCGGCAGCC**ATG**CGGTGGAAGGAGGAATGAAATGTGTGAAGTTCTGCTCTACGTCCCTGCT
GGCCTTTGCGCCTGTGCAGTGGACTGATTGCCGTGGGTGTCGGGGCACAGCTGTCTGAGTCAGACCATAAT
CCAGGGGGCTACCCCTGGCTCTGTTGCCAGTGGTCATCATCGCAGTGGGTGTCCTCCTCTGGCTTGGCTT
TGTGGGCTGCTGCCGGGCTGCAAGGAGAACTATTGTCTTATGATCACGTTGCCATCTTCTGTCTCTTATCAT
GTTGGTGGAGGTGGCCGCAGCCATTGCTGGCTATGTGTTAGAGATAAGGTGATGTCAGAGTTAATAACAACTT
CCGGCAGCAGATGGAGAATTACCGAAAAACAAACCACACTGCTTCGATCCTGGACAGGATGCAGGCAGATTTAA
GTGCTGTGGGCTGCTAATGTTACTGTGGGCTGTGGGATTAATTCAACGAGAAGGCATCCATAAGGAGGGCTGTGGAGAA
GATTGGGGCTGGCTGAGGAAAAATGTGCTGGTAGCTGCAGCAGCCCTTGGATTGCTTTGTCAGAGGTTT
GGGAATTGTCTTGCCTGCTGCCTCGTAAGAGTATCAGAAGTGGCTACGAGGTGATG**TAG**GGGTCTGGCTCCT
CAGCCTCCTCATCTGGGGAGTGAATAGTATCCTCCAGGTTTCAATTAAACGGATTATTTTCAGACCGAA
AAGAAAAAAAAAAAAAA

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FIGURE 89

MAVEGGMKVKFLLYVLLL AFCACAVGLIAVGVGAQLVLSQTIIQGATPGSLLPVVIIAVGVFLFLVAFVGCCGA
CKENYCLMITFAIFLSLIMLVEAAAIAGYVFRDKVMSEFNNNFRQQMENYPKNNHTASILD RMQADF KCCGAAN
YTDWEKIPSMSKNRVPDSCCINVTVGCGINFNEKAIHKEGCVEKIGGWL RKNVLVVAAAALGIAFVEVLGIVFAC
CLVKSIRSGYEVM

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FIGURE 90

CGGGAGAGCGCGCTGCCTGCCCTGCCACTGAGGGTCCCAGCACCATGAGGGCTGGATCTTC
TTTCTCCTTGCCTGGCGGGAGGGCTTGGCAGCCCTCAGCAAGAAGCCCTGCCATGAGACAGAGGTGGT
GAAGAAACTGTGGCAGAGGTGACTGAGGTATCTGTGGAGCTAATCCTGTCCAGGTGGAAAGTAGGAGAATTGAT
GATGGTGCAGAGGAACCGAAGAGGAGGTGGTGGCGAAAATCCCTGCCAGAACCAACTGCAAACACGGCAAG
GTGTGCGAGCTGGATGAGAACACACCCCCATGTGCGTGTGCCAGGACCCACCAGCTGCCAGCCCCATTGGC
GAGTTGAGAAGGTGTGCAGCAATGACAACAAGACCTCGACTCTCCTGCCACTTCCACAAAGTGCACC
CTGGAGGGCACCAAGAAGGGCACAGCTCCACCTGGACTACATGGGCCTGCCAAATACATCCCCCTGCCTG
GACTCTGAGCTGACCGAATTCCCCCTGCGCATGCCAGTGGACTGGCTCAAGAACGTCTGGTACCCCTGTATGAGAGG
GATGAGGACAACAACCTCTGACTGAGAACAGCAGAACAGCTGCCAGTGGACTGGCTCAAGAACGTCTGGTACCCCTGT
GAGGCAGGAGACCACCCCTGGAGCTGCTGCCAGTGGACTTCGAGAACACTATAACATGTACATCTCCCTGTA
CACTGGCAGTCGCCAGCTGGACCAGCACCCATTGACGGTACCTCTCCACACCGAGCTGGCTCCACTGCGT
GCTCCCCATCCCCATGGAGCATTGACACCACCGCTTTCAGACGGTACCTGTGACCTGGACAATGACAAGTACATC
GCCCTGGATGAGTGGCCGGCTGCTCGGCATCAAGCAGAACGGATATCGACAAGGATCTTGTGATCTAAATCCAC
TCCTTCCACAGTACCGGATTCTCTCTTAACCTCCCTCGTGTTCCTTAAATGTTAAATGTTGGATGGT
TTGTTGTTCTGCCCTGGAGACAAGGTGTAACATAGATTAAAGTGAATACATTAACGGTGTAAAATGAAAATT
TAACCCAAGACATGACATTCTAGCTGTAACTTAACCTATTAGGCCTTCCACACGCATTAATAGTCCCATT
TCTCTGCCATTGTAGCTTGCCTATTGTCATGGCACATGGGTGGACACGGATCTGCTGGCTCGCCTTA
AACACACATTGCACTTCACCTTCTCTTAGTGTCTGGTAAACTAATACCTACCGAGTCAGACTTGT
TCATTTCAATTGAGGGCTTGGCTGCCGTGGCTTCCCCAGGTGGCTGGAGGTGGCAAAGGGAAAGTAACAGA
CACACGATGTTGTCAGGATGGTTTGGGACTAGAGGCTCAGTGGTGGAGAGATCCCTGCAAAATCCACCAACC
AGAACGTGGTTGCTGAGGCTGTAACTGAGAGAACAGATTCTGGGCTGTCTTATGAAAATATAGACATTCTCAC
ATAAGCCCAGTTCATCACCAATTCTCTTTACCTTCAGTCAGTTCTTACATTAGGCTGTTGGTCAAA
CTTTGGGAGCACGGACTGTCAGTTCTGGAAAGTGGTCAAGCAGCCTCTGCAGGGCTTCTCCTCTGTCTT
TGGAGAACAGGGCTTCTCAGGGCTCTAGGGACTGCCAGGCTGTTCAAGCAGGAAGGCCAAAATCAAGAGT
GAGATGTAGAAAGTTGTAAAATAGAAAAAGTGGAGTTGGTGAATGGTCTTCTCACATTGGATGATTG
TCATAAGGTTTGTAGCATGTCCTCCTTCTCACCCCTCCCTTGGTCTTCTATTAAATCAAGAGAAACTTC
AGTTAATGGGATGGTGGATCTCACAGGCTGAGAACCTGTTCACCTCAAGCATTCATGAAAAGCTGCTT
ATTAATCATACAAACTCTCACCATGATGTGAAGAGTTCACAAATCTTCAAAATAAAAGTAATGACTTAGAAA
CTGAAAAAAAAAAAAAAAAAAAAAA

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FIGURE 91

MRAWIFFLLCLAGRALAAPQQEALPDETEVVEETVAEVTEVSVGANPVQVEVGEFDDGAEETEEEVVAENPCQNH
HCKHGKVCELDENNTPMCVCQDPTSCPAPIGEFEKVCSDNDNKTFDSSCHFFATKCTLEGTKKGHLHLDYIGPCK
YIPPCLDSELTEFFPLMRDWLKNVLVTLYERDEDNNLLTEKQKLRVKKIHENEKRLEAGDHPVELLARDFEKNYN
MYIFPVHWQFGQLDQHPIDGYLSHTELAPLRAPIPMEHCTRFFETCDLDNDKYIALDEWAGCFGIKQKDIDKD
LVI

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FIGURE 92

CCGGCCCGCGCCCCGAGGCCGCCGCCGCCGCCGCCATGGGAGTGGAGGGCTGCACCAAGTGCATCAAGTA
CCTGCTCTCGTCTCAATTCTGCTTCTGGCTGGCTGGAGCGTGATCCTGGGTGTGGCCCTGTGGCTCCGCCA
TGACCCCGCAGACCACCAACCTCCTGTATCTGGAGCTGGAGACAAGCCCGCGCCAACACCTCTATGTAGGCAT
CTACATCCTCATCGCTGTGGCGCTGTCATGATGTTGTTGGCTTGGCTGCTACGGGCCATCCAGGAATC
CCAGTGCCTGCTGGGACGTTCTCACCTGCCTGGTATCCTGTTGCCTGTGAGGTGGCCCGGCATCTGGGG
CTTGTCACAAGGACCAGATGCCAAGGGATGTGAAGCAGTTCTATGACCAGGCCCTACAGCAGGCCGTGGTGG
TGATGACGCCAACACGCCAAGGCTGTTGAAGACCTTCCACGAGACGCTTGACTGCTGTGGCTCCAGCACACT
GACTGCTTGACCACCTCAGTGCCTAAGAACATTGTCCTCGGGCAGCAACATCATCAGCAACCTCTCAA
GGAGGACTGCCACCAAGATCGATGACCTCTTCGGGAAGCTGTACCTCATGGCATTGCTGCCATCGTGGT
CGCTGTGATCATGATCTCGAGATGATCCTGAGCATGGTGTGCTGGCATCGGAACAGCTCCGTGTACTG
AGGCCCCGAGCTCTGCCACAGGGACCTCTGCAGTGCCCCCTAAGTGACCCGGACACTCCGAGGGGCCATCA
CCGCCTGTGTATAACGTTCCGGTATTACTCTGCTACACGTAGCCTTTACTTTGGGTTTGTTGTT
CTGAACCTTCCTGTTACCTTCAGGGCTGACGTACATGTAGGTGGCGTGTATGAGTGGAGACGGGCCTGGGTC
TTGGGGACTGGAGGGCAGGGTCTCTGCCCTGGGTCCCAGGGTGTCTGCCCTGCTCAGCCAGGCCCTCCTG
GGAGCCACTGCCAGAGACTCAGCTGGCCAACCTGGGGCTGTGTCCACCCAGCCGCCGTCCTGTGGGCT
GCACAGCTCACCTGTTCCCTGCCGGTTGAGAGCCGAGTCTGTGGCCTCTGCCATGCACCTG
TCCTTCTAACACGTCGCCCTCACTGTAATCACAACATCCTGACTCCGTATTAAATAAGAAGGAACATCAGG
CATGCTAA

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FIGURE 93

MGVEGCTKCIKYLLFVFNFVFWLAGGVILGVALWLRHDPQTNTLLYLELGDKPAPNTFYVGIVIYILIAVGAVMMFV
GFLGCYGAIQESQCLLGTFFTCLVILFACEVAAGIWGFVNKDQIAKDVKQFYDQALQQAVVDDDANNAKAVVKTF
HETLDCCGSSTLTALTTSVLKNNLCPSGSNIISNLFKEDCHQKIDDLFSGKLYLIGIAAIVVAVIMIFEMILSMV
LCCGIRNSSVY

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FIGURE 94A

GCTAAGTTAGCTTCACTGGCACTGTATGGCAGCATTGGTATGGTAGCGTGGCACATGGCGAACATAA
 AGCATTACTGTACAGGAATGTGCCATGTCTTACCTATCTCTCTCACTCCCATGCACAC
 ATCCTGTGTATTAGAGACCTCAGAAACATTCAATTCAATTGAGTCAGCAAAAGCCATGCTGAT
 TCCAACAGAAATATTCCCTTACATACTTCTCTTAATTTCAGAAATTGTATGGTAGGTGAAAGAAAAT
 CATAGTAACTGTACCATATTATAACCCCTAAATCAAACATTGGTGTATCTGATCTGTTCTGTC
 TTTATAGTGAAGCAGCCGACACGAGTCGTTGTCATAAAACAGCTTGAAGAGAGCACACCCCTGGAGAA
 CCGACTGTGCTTGTACGTTGGTCACTGACTAAAATCAGTACAGGTGATGAAATCTGGCAGTGTAAACA
 AAAAGTAGTGTATTGTCTATTCTAGAAACCTAACATTGTAGAGAAAAGGAAACAAAT
 TTCACACATTGAAGTTCAATTGACATAAAATTATGATAAATAATCATAGAAATCAAGCTTGTATTAGCG
 AACATAAGTACTTCAACAAACTCAGGGGTGATCAGGGAGACATTCTGGGTTGTGTTCTGTC
 TTAGAAAAGAATGTGTTCAATGCAAGGATGTTCTGCAAGGAGTTATTGATGAAGCTAAAGCTTGTCTC
 TGTTGGCACAGCTAATGCACTGGCAGGTCTGCCTGGTGGACTCCTGCCTACTCCTAACCCACTTACCC
 AGATTGGCGCTGTTCCACTGGCTGCTTGGGGCTCCTACTCTGATCCTGCCCTGCTGCACTGGGCTCCTG
 GAGCAAACCTGAACCTCAGTCTTGCTGAGATCAGTTGCTGAAGCTTATGAGTACTGTTGATCCAAGTTGA
 ATCATGTAGCTGCTGGCTCGTTACCAAGTCTGAAATGGATAACCTCTAGTAAAGAAATAGAGGAAGCTATGA
 AAAGAGTACGAGAACGACAGTCCCTAATTCTGCTGCTATAAGAACAGATAAGAAGAAAAGAACAGGATT
 CAAGATCAAGATCACGTTCTAGGAGGAGGACTCCCTCATCTCTAGACACAGCGGTCAAGAACAGATCGA
 GACGGCGGTACATTCTAAGTCTAGGAGTCGGCAGATCCAAAAGCCAAGGCGGAGAACATCTCATTCCAGAG
 AAAGAGGTAGAAGGTCAAGGAGCACATAAAAACAGAGACAAAAAGAAAGAACAAAGAACAGTTCTA
 AAACACCACAAAAGTTACAGCACAGCCAGACGTTCTAGAAGTGAAGCAGAGTATATTGAAGTAACATGGAA
 TTCAAGAGAGAGAGACGACGAAGAAGCAGGAGTGGCACAAGATCTCTAAAAGCCTCGGTCTCTAAAA
 GAAAATTGTCGCTCACCATCCCCTAGGAGACATAAAAGGAGAAGAAGAAAGATAAGAACAAAGAACAGTA
 GGGATGAAAGAGAACGATCAACAAGCAAGAAGAAGAGTAAAGATAAGGAAAGGACCGGGAAAGAAAATCAG
 AGAGTGATAAAGATGTTAAACAGGTTACACGGGATTATGATGAAGAGGAACAGGGGTATGACAGTGAGAAAGAGA
 AAAAGAAGAGAACCAATAGAACAGGTTCCCTAAAACAAAGGAATGTTCTGTTGAAAGGAACGGTGTG
 ATTCAACTAAGAACATCCAAAGTGAATGGGATGATCATCATGAAGAACATGGATATGAGTGAATATTG
 CTCTGAGGGAGTCCAACGTGATACCTGCATCAGTGTCTTGTGATTCTTAATGCTGTATTGTCAT
 CTCAAACCTAGATGTATACAGCTCTGAGTTAAAGCTCTGTTACTCATATTAGTTATTACAT
 CAAAAAGCTTTAGAAAATGGTACGAGGTAACCAATTCTGATGGAAATCTGATTGAGTAACCAAGCAGTT
 TTACTATTCTGGTCTGCTTCATAACAAAATGAAAGCTGCATGCATCTACAGCAGGATGGATTGTTATGTC
 GTATGATATCCTTATTAAGTAAGTCACTTATAGTATTCTATAATTGATTGATCTGCCGTAATAGAGCCATG
 AGGAAATGCACTGATTGATCTTGTGCAAGAACATCTAAATGTCATTAAACCTCCAACATGATGGATC
 TACTTATGGCTTGTGACATGACAAATTACATTCTATAGTTACATCTGAAATGAGCATTTGAAATAG
 ATAATCCTTAAGCCTGTGCAAAATTGTTGTGCTTTGTTAACTTGAAAGGTATTATGCACTAACCTTT
 TTTGGTGGCTAATTAGGTTAAACAGAACAGATTCTAAACTGTCTTGGCAGTGTGAGTAATAGCA
 TATTGAAAGTAGAGTTGATACCTTCTATAAGATGTTGGGAAATTCTGAAAGTAATAATTATTCCAC
 ATCTACATCAGTGAAGCTATCTACCTATCTGAGTCTATCTAAAGGAAAAAGAAAAACCTTATCTCTG
 CCCTTATTGAAATTCTACGCTTAAAATAGAACAAATCTACTGATAATGTCACCTTGTGAAAGGGTAGTGCATT
 AAATTGACCTCATACTGCTTAAAATAGAACAAATCTACTGATAATGTCACCTTGTGAAAGGGTAGTGCATT
 AAAACCAATAATTGTTACTGCACTGAGTAGTAATCTTACGACACGGTGTGTTGAAAGCTACAGTCTGTG
 CAACTGTTCTAGTTACAGAAGTTCAAGCTTCACCTTGTGCACTGAGTAGAACACAAAGTAGGCTACAGTCTGTG
 CCATGTTGATGTACAGTTCTGAAATTGTTACAAGACTTGTGATAATAACCCCTAAACCTTATGTCATGTT
 CTGAAAACCGTATTGTTACTGCTACTGAAATGTCACCTCATTCAAAATTCTTCTGAAAGGGTAGTGCATT
 CCTTCTGTCACATATTGAGTAAAGAGGAAAGTCTATCAGTGTAGTGTATAATTGCCATCAAATTG
 CAAAATGATTAAATTCTATCCAAAATAGTCCTTCTAGCTAGTATCATTGCTTATTGCTTATTGTTGTG
 GGAATGGGTTGGATAAGCAATGAACTTAGTATAAACAAATCCCACCTATATGCAAAATTATTTGCG
 TGAAATACAGATATTGCTTCTGGAGTAGTATAGAACAGTGTCAATATGTTACTGTACAGTAAATAGT
 ATTCAATTGAAATGAGTAGTGTGTTGGTGGCTGGGTTAAGGGAAAATGAGACTTGGAAATTGAGCTTAC

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FIGURE 94B

CAAGTTTGAGTATAAATAGGGTTTGTCCCCCTAACCTAAAAACTGAAATGCCATATAGAAAAACAGC
ATTGTTTTACAGTTGTAGTAAGTAACCTTTAAAGATTTATCAAAAAGAATTGTCTATAGTGAGTAAAG
AAGTTCTAATAATGGTCCTAATCACTGCATTTAAAAAACAAAGTCAACACAAATGACATTGTTAAACTT
TAGTAGATAAAAGGTGAACCATGTGACATGGCATTGTAAAGTCAAAACAAATTACATGGTAAACCTA
ATATTCACAGTGTGTTCCCTCACTTGTAAATCTCTGAATACAAATATACTAGCTTCTAAAGGGAAATCATT
TAAAAGTAGTGCCACTGACAAGATGCTACAGTGAAGATTATCCATTCTAGGATATTATTCAGTGAACATT
TCTGCACAAAGGTAGTGTGCACTGGGACACAAGCCTTTAACAGATAACCAGTTGAAATCAAACACTGCCTCCA
CACCGAGTTCTGTTGTATTGATAGTAAATTGATTAAAAAGTGGTTTGTAGAAA

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FIGURE 95

MINNHRNQALYFSEHKYFOOTQVYQGDIFWVFLCVFCLRKECVLMQGCF SAGVIPDEAKALSLLAPANAVAGLL
PGGGLLPTPNPLTQIGAVPLAALGAPTLDPALAALGLPGANLNSQSLAADQLLKLMSTVDPKLNHVAAGLVSPSL
KSDTSSKEIEEAMKRVREAQSLISAAIEPDKKEEKRRHSRSRSRRRTPSSSRHRRSRSSRSRRSHSKRSRSRR
RSKSPRRRRSHSRERGRRSRSTSCTRDKKEDKEKKRSKTPPKSYSTARRSRSA SRVYLK

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FIGURE 96

GGCACGAGGGAGCGCTTGTGCTGCCCGTACTCCCTCATTATCCGCCATGATAAGTGCCAGCCGAGCTGCA
GCAGCCCGTCTGGCGCCGCAGCCTCCGGGCCCTACGGCCGCCGCCACAGGATAGCTGGAATGGCCTT
AGTCATGAGGCTTTAGACTTCAAGGCAGGATTATGCATCAGAAGCAATCAAGGGAGCAGTTGTTGGTATT
GATTGGGTACTACCAACTCCTGCGTGGCAGTTATGGAAGGTAAACGAGCAAAGGTGCTGGAGAATGCCGAAGGT
GCCAGAACCCCCCTCAGTTGTGGCCTTACAGCAGATGGTGAGCAGTTGGAATGCCGCCAAGCGACAG
GCTGTCACCAACCCAAACAATACATTATGCTACCAAGCGTCTCATTGGCGGCATATGATGATCTGAAGTA
CAGAAAGACATTAAAATGTCCTTAAAATTGTCCTGCCATGGTGATGCTGGGTGAGGCTATGGG
AAATTGATTCTCGAGTCAGATTGGAGCATTTGTGTTGATGAAAGATGAAAGAGACTGCAGAAAATTACTGGGG
CGCACAGAAAAATGCTGTGATCACAGTCCCAGCTTATTCAATGACTCGCAGAGACAGGCCACTAAAGATGCT
GGCCAGATATCTGGACTGAATGTGCTCGGGTGATTATGAGCCCACAGCTGCTGCTTGCCTATGGCTAGAC
AAATCAGAACAGAACAGTCATTGCTGTATATGATTAGGTGGAAACTTTGATATTCTATCCTGGAAATTCA
AAAGGAGTATTGAGGTGAAATCCACAAATGGGATACCTCTTAGGTGGGAAGACTTTGACCAGGCCCTGCTA
CGGCACATTGTGAAGGAGTTCAAGAGAGAGACAGGGGTTGATTGACTAAAGACAACATGGCACTTCAGAGGGTA
CGGGAAAGCTGCTGAAAAGGCTAAGTGTGAACTCTCCTCATTGTGAGACTGACATCAATTGCCCTATCTTACA
ATGGATTCTCTGGACCCAAAGCATTGAAATATGAAAGTTGACCCGTGCTCAATTGAAAGGATTGTCACTGATCTA
ATCAGAAAGGACTATCGCTCCATGCCAAAAGCTATGCAAGATGCAAGACTGACAGACTGACATAGGAGAAAGT
ATTCTTGTGGGTGGCATGACTAGGATGCCAAGGTTCAGCAGACTGTACAGGATCTTGGCAGAGCCCCAAGT
AAAGCTGCAATCCTGATGAGGCTGTGGCATTGGAGCTGCCATTAGGGAGGTGTTGCCGGCATGTCACG
GATGTGCTGCTCTTGATGTCACTCCCTGCTCTGGTATTGAAACTCTAGGAGGTGTTACCAAACATTATT
AATAGGAATACCAACTATTCCAACCAAGAAGAGGCCAGGTATTCTACTGCCGCTGATGGTCAAACGCAACTGGAA
ATTAAAGTGTGTCAGGGTGAAAGAGAGATGGCTGGAGACAACAAACTCCTGGACAGTTACTTGTGATTGGAAATT
CCACCAGCCCCCTGTGGAGTTCTCAGATTGAAGTTACATTGACATTGCAATGGGATAGTACATGTTCT
GCTAAAGATAAAGGCACAGGACGTGAGCAGCAGATTGTAATCCAGTCTCTGGTGGATTAAGCAAAGATGATATT
GAAAATATGGTTAAAATGCAGAGAAATATGCTGAAGAAGACCGGCGAAAGAAGGAACGAGTTGAAGCAGTTAAT
ATGGCTGAAGGAATCATTACGACACAGAACCAAGATGGAGAATTCAAGGACCAATTACCTGCTGATGAGTGC
AACAAAGCTGAAAGAAGAGATTCCAAGGAGCTCTGGCTAGAAAAGACAGCGAAACAGGAGAAAATATT
AGACAGGCAGCATCCTCTTCAAGGGCATATTGAAGCTGTTGAAATGGCATAACAAAAGATGGCATCTGAG
CGAGAAGGCTCTGGAAGTTCTGGCACTGGGAACAAAAGGAGATCAAAGGAGGAAAACAGTAAAATAGCAG
AAATTGAAAGCCAGAAGGACAACATATGAAGCTTAGGAGTGAAGAGACTCTGAGCAGAAATGGCGAACCTC
AGTCTTTTACTGTGTTTGCACTATTCTATATAATTCTTAATTGTAATTAGTCAACAGTATAAAGGTTCAA
GATCATTAATGGACAGTGAATTCTAACAGTATAAAGGTTCAAATATTCTATGTCCTAGCTGTCATTTCAGC
TGCATGAAAAGGAGGTTAGGATGAATTGATCATTATAAAGATTAAACTATTATGCTGAAGTGAACGATATTTC
AAGGGGTGAAACCACATCTGCACACAGCAATGAAGGTAGTCATCCATAGACTTGAAATGAGACCAATATGGGGAT
GAGATCTCTAGTTAGCCTAGTACTGCTGACTGGCCTGATGTACATGGGGCCTCAACTGAGGCCCTGCAA
GTCAAGCTGGCTGTGCCATGTTGAGATGGGGCAGAGGAATCTAGAACAAATGGGAAACTTAGCTATTATATT
GGTACAGCTATTAAAACAAGGTAGGAATGAGGCTAGACCTTAACTTCCCTAAGGCATACTTTCTAGCTACCTT
CTGCCCTGTGCTGGCACCTACATCCTGATGATTGTTCTTACCCATTCTGGAAATTTTTTTTAAATA
AATACAGAACAGCATCTGAAAAAAAAAAAAAA

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FIGURE 97

MISASAAAARLVGAAASRGPTAARHQDSWNGLSHEAFRLVSRRDYASEAIKGAVVGIDLGTTCVAVMEGKRA
KVLENAEGARTTPSVVAFTADGERLVMGMPAKRQAVTNPNNTFYATKRLIGRRYDDPEVQKDICKNVPFKIVRASNG
DAWVEAHGKLYSPSQIGAFVLMKMKETAENYLGRATAKNAVITVPAYFNDSSQRQATKDAGQISGLNVLRVINEPTA
AALAYGLDKSEDKVIAVYDLGGGTFDISILEIQKGVFEVKSTNGDTFLGGEDFDQALLRHIVKEFKRETGVDLTK
DNMALQRVREAAEKCELSSVQTDINLPYLTMDSSGPKHLNMKLTRAQFEGIVTDLIRRTIAPCQKAMQDAEV
SKSDIGEVILVGGMTRMPKVQQTVQDLFGRAPS KAVNPDEAVAIGAAIQGGVLAGDVTDVLLDVPLSLGIETL
GGVFTKLINRNTTIPTKKSQVFSTAADGQTQVEIKVCQGEREMAGDNKLLGQFTLIGIPPA PRGVPQIEVTFDID
ANGIVHVSADKKGTRQQIVIQSSGGLSKDDIENMVKNAAEKYAEEDRRKKERVEAVNMAEGIIHDTEKMEEFK
DQLPADECNKLKEEISKMRELLARKDSETGENIRQAASSLQQASLKFEMAYKKMASEREGSGSSGTGEQKEDQK
EEKQ

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FIGURE 98

GGCACGAGGGAGCGTTGTTGCTGCCCGTACTCCTCCATTATCCGCCATGATAAGTGCCAGCCGAGCTGCA
 GCAGCCCGTCTCGTGGCGCCCGAGCCTCCCAGGGCCCTACGGCCGCCACCAGGATAGCTGGAATGGCCTT
 AGTCATGAGGCTTTAGACTGTTCAAGGCGGGATTATGCATCAGAACATCAAGGGAGCAGTTGTTGGTATT
 GATTTGGGTACTACCAACTCCTGCGTGGCAGTTATGGAAGGTAAACGAGCAAAGGTGCTGGAGAATGCCAAGGT
 GCCAGAACCAACCCCTCAGTTGTCGCTTACAGCAGATGGTGAGCAGCTTGTGGAATGCCGCCAAGCAGACAG
 GCTGTCACCAACCCAAACAATACATTATGCTACCAAGCGCTCATGGCCGGCATATGATGATCCTGAAGTA
 CAGAAAGACATTAAGGTTCCCTTAAATTGTCGTCGCTCCAATGGTGTGATGCCCTGGGTGAGGCTCATGGG
 AAATTGATTCTCGAGTCAGATTGGAGCATTGTTGATGAAGATGAAAGAGACTGCAGAAAATTACTGGGG
 CGCACAGCAAAATGCTGTGATCACAGTCCCAGCTATTCAATGACTCGCAGAGACAGGCCACTAAAGATGCT
 GGCCAGATATCTGGACTGAATGTGCTCGGGTGTATTATGAGGCCACAGCTGCTGCTTGCCTATGGCTAGAC
 AAATCAGAAGACAAAGTCATTGCTGATATGATTAGGTGGAACTTTGATATTCTATCCTGAAATTCA
 AAAGGAGTATTGAGGTGAAATCCACAAATGGGATACTTCTAGGTGGGAAGACTTGCACAGGCCCTGCTA
 CGGCACATTGTGAAGGAGTTCAAGAGAGACAGGGGTGATTGACTAAAGACAACATGCCACTTCAGAGGGTA
 CGGGAAAGCTGCTGAAAGGCTAAGTGTGAACTCTCTCATCTGTGCAACTGACATCAATTGCCCTATCTTACA
 ATGGATTCTCTGGACCCAAAGCATTGAATATGAAGTTGACCCGTGCTCAATTGAAGGGATTGTCAGTCA
 ATCAGAAGGACTATCGCTCCATGCCAAAAGCTATGCAAGATGCAAGACTGACATCAAGAGACTGACATAGGAGAAGTG
 ATTCTTGTTGGTGGCATGACTAGGATGCCAAGGTTGAGCAGACTGTACAGGATCTTTGCAAGGCCCAAGT
 AAAGCTGTCATCCTGATGAGGCTGTGCCATTGGAGCTGCCATTAGGGAGGTGTGGCCGGCATGTCACG
 GATGTGCTGCTCCTGATGTCACTCCCCGTCTCTGGTATTGAAACTCTAGGAGGTGTCTTACAAACTTATT
 AATAGGAATACCAACTATTCAACCAAGAACAGGCCAGGTATTCTACTGCGCTGATGGTCAAACGCAAGTGGAA
 ATTAAAGTGTGTCAGGTGAAAGAGAGATGGCTGGAGACAACAAACTCCTGGACAGTTACTTGATGGAATT
 CCACCAGCCCCTCGGAGTTCTCAGATTGAAGTTACATTGACATTGATGCCAATGGGATAGTACATGTTCT
 GCTAAAGATAAAGGCACAGGACGTGAGCAGCAGATTGTAATCCAGTCTCTGGGATTAAGCAAAGATGATATT
 GAAAATATGGTAAAGGCAAGAGAAATATGCTGAAGAAGACCGGGCAAAGAAGGAACGAGTTGAAGCAGTTAAT
 ATGGCTGAAGGAATCATTACGACACAGAAACCAAGATGGAAGAATTCAAGGACCAATTACCTGCTGATGAGTGC
 AACAAAGCTGAAAGAAGAGATTCCAAAATGAGGGAGCTCTGGCTAGAAAAGACAGCAGAAACAGGAGAAAATATT
 AGACAGGCAGCATCCTCTTCAGCAGGCATCATGAAAGCTGTCGAAATGGCATAACAAAGATGGCAGTCTGAG
 CGAGAAGGCTCTGGAGTTCTGGCACTGGGAACAAAGGAAGATCAAAGGAGGAAAACAGTAAATAATAGCAG
 AAATTGAAAGCCAGAAGGACAACATATGAAGCTAGGAGTGAAGAGACTCCTGAGCAGAAATGGCGAACTTC
 AGTCTTTACTGTGTTTGCACTATTCTATATAATTCTTAATTGTAATTTAGTGACCAATTAGCTAGT
 GATCATTAAATGGACAGTGATTCTAACAGTATAAAGTTCAACATATTCTATGCTCTAGCCTGTCATTTCAGC
 TGCATGIAAAAGGAGGTAGGATGAATTGATCATTATAAAGATTAACTATTGCTGAAGTGCACATTTC
 AAGGGGTGAAACCATCTGCACACAGCAATGAAGGTAGTCATCCATAGACTGAAATGAGACCAACATGGGGAT
 GAGATCCTCTAGTTAGCCTAGTACTGCTGACTGGCCTGTTACATGGGGCTTCAACTGAGGCCCTGCAA
 GTCAAGCTGGCTGTGCCATTGTTGAGATGGGGCAGAGGAATCTAGAACAAATGGGAAACTTAGCTATTATTA
 GGTACAGCTATTAAACAAAGGTTAGGAATGAGGCTAGACCTTAACCTCCATAAGGCATACTTTCTAGCTACCTT
 CTGCCCTGTCGGCACCTACATCCTGATGATTGTTCTTACCCATTCTGGAATTTTTTTTAAATA
 AATACAGAAAGCATCTGAAAAA

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FIGURE 99

MISASAAAARLVGAAASRGPTAARHQDSWNGLSHEAFRLVSRDYASEAIKGAVVGIDLGTTCVAVMEGKRA
KVLENAEGARTTPSVVAFTADGERLVGMPAKRQAVTNPNNTFYATKRLIGRRYDDPEVQKDICKNVPFKIVRASNG
DAWVEAHGKLYSPSQIGAFVLMKMKETAENYLGRITAKNAVITVPAYFNDSQLQATKDAGQISGLNVLRVINEPTA
AALAYGLDKSEDKVIAVYDLGGGTFDISILEIQKGVFEVKSTNGDTFLGGEDFDQALLRHIVKEFKRETGVDLTK
DNMALQRVREAAEKCELSSVQTDINLPYLTMDSSGPKHLNMKLTRAQFEGIVTDLIRRTIAPCQKAMQDAEV
SKSDIGEVILVGGMTRMPKVQQTVDLGRAPSKAVNPDEAVAIGAAIQGGVLAGDVTDVLLDVTPLSLGIETL
GGVFTKLINRNTTIPTKKSQVFSTAADGQTQVEIKVCQGEREMAGDNKLLGQFTLIGIPPAVRGPQIEVTFDID
ANGIVHVSADKGTGREQQIVIQSSGGLSKDDIENMVKNAAEKYAEEDRRKKERVEAVNMAEGIIHDTETKMEEFK
DQLPADECNLKKEEISKMRELLARKDSETGENIRQAASSLQQASLKFEMAYKKMASEREGSGSSGTGEQKEDQK
EEKQ

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FIGURE 100

GGCGTGTGCCACCATGGCTCCGACCGCCCCCGCGCCGCTGCTTGCGCGTGTCCCTGGCGCTGTGCGCGC
TGTCGCTGCCGTCCGCGGCCACTGCGTCGCGGGGGCGTCCCAGGCGGGGCGCCCAAGGGCGGGTGCCCG
AGGCGCGGCCAACAGCATGGTGGAGAACACCCGAGTCTCTCAAGGCAGGGAAAGGAGCCTGGCCTGCAGATCT
GGCGTGTGGAGAAGTTGATCTGGTCCCCGTGCCAACCAACCTTATGGAGACTTCTTCACGGCGACGCCCTACG
TCATCCTGAAGACAGTGCAGCTGAGGAACGAAATCTGCAGTATGACCTCAACTGGCTGGCAATGAGTGCA
GCCAGGATGAGAGCAGGGCGGCCATCTTACCGTGCAGCTGGATGACTACCTGAACGGCGGGCGGTGCAGC
ACCGTGAGGTCCAGGGCTTCGAGTCGCCCCACCTCCTAGGCTACTTCAAGTCTGGCCTGAAGTACAAGAAAGGAG
GTGTGGCATCAGGATTCAAGCACGTGGTACCCAACGAGGTGGTGGTGCAGAGACTCTTCCAGGTCAAAGGGCGGC
GTGTGGTCCGTGCCACCGAGGTACCTGTGCTGGAGAGCTCAACAATGGCAGTGCTTCATCCTGGACCTGG
GCAACAAACATCCACCAGTGGTGTGGTCCAACAGCAATCGGTATGAAAGACTGAAGGCCACACAGGTGTCCAAGG
GCATCCGGACAACGAGCGGAGTGGCCGGCCGAGTGCACGTGTCTGAGGAGGGCACTGAGCCGAGGCGATGC
TCCAGGTGCTGGGCCAACGCCGCTCGCCTGCAGGTACCGAGGACACCGCAAGGAGGATGCGGCCAACCGCA
AGCTGGCCAAGCTCTACAAGGTCTCCAATGGTCAGGGACCATGTCCGTCTCCCTCGTGGCTGATGAGAAACCCCT
TCGCCCAGGGGCCCTGAAGTCAGAGGACTGCTTCATCCTGGACCACGGCAAAGATGGAAAATCTTGTCTGGA
AAGGCAAGCAGGCAAACACGGAGGAGAGGAAGGCTGCCCTCAAAACAGCCTCTGACTTCATACCAAGATGGACT
ACCCCAAGCAGACTCAGGTCTCGGTCTTCCCTGAGGGCGGTGAGACCCACTGTTCAAGCAGTCTCAAGAAACT
GGCGGGACCCAGACCAGACAGATGGCTGGCTTGTCTACCTTCCAGCCATATGCCAACGTGGAGCGGGTG
CCTTCGACGCCGCCACCTGCACACCTCACTGCCATGGCCGCCAGCACGGCATGGATGACGATGGCACAGGCC
AGAAACAGATCTGGAGAATCGAAGGTCCAACAAAGGTGCCCTGCCACATATGGACAGTTCTATGGAG
GCGACAGCTACATCATTCTGTACAACCTACCGCCATGGTGGCCGAGGGCAGATAATCTATAACTGGCAGGGTG
CCCAGTCTACCCAGGATGAGGTGCTGCATCTGCATCTGACTGCTCAGCTGGATGAGGAGCTGGAGGTACCC
CTGTCCAGAGCGTGTGGTCCAAGGCAAGGAGCCGCCACCTCATGAGCCTGTTGGTGGAGGCCATGATCA
TCTACAAGGGCGGCACCTCCCGAGGGCGGGCAGACAGCCCTGCCAGCACCCGCCCTTCCAGGTCCCGGCCA
ACAGCGCTGGAGCCACCCGGCTGTTGAGGTATTGCTTAAGGCTGGTGCAGTGAACCTCAACGATGCCCTTGT
TGAAAACCCCTCAGCCGCTACCTGTGGTGGGTACAGGAGCCAGCGAGGCAGAGAAGACGGGGGCCAGGAGC
TGCTCAGGGTGTGCGGGCCCAACCTGTGCAGGTGGCAGAAGGCAGCGAGCCAGATGGCTCTGGAGGCCCTGG
GCAGGGAGGCTGCCCTACCGCACATCCCCAGGCTGAAGGACAAGAAGATGGATGCCATCTCCCTGCCCTTGT
CTGCTCCAACAAGATTGGACGTTGTGATCGAAGAGGTTCTGGTGAGCTCATGCAGGAAGACCTGCCAACGG
ATGACGTATGCTCTGGACACCTGGACCAGGTCTTGCTGGTTGGAAAGGATTCTCAAGAAGAAGAAAAGA
CAGAAGCCTTGACTCTGCTAACGGTACATCGAGACGGACCCAGCCAATCGGGATGGCAGGCCATCACCG
TGGTGAAGCAAGGCTTGAGGCTCCCTCTTGTGGCTGGTCTGGCTGGATGATGATTACTGGCTGTGG
ACCCCTGGACAGGGCATGGCTGAGCTGGCTGCTGAGGAGGGCAGGGCCCACCCATGTCACCGGTAGTGCC
TTTGGAACTGCTCTCCCTAAAGAGGCCCTAGAGCGAGCAGGCAGTCTGCTATGAGTGTGTGTGT
GTGTGTTCTTTTTTACAGTATCAAAAATAGCCCTGCAAAATTAGAGTCCTGCAAAATTGTC
TAAAATGTCAGTGTGTTGGAAATTAAATCCAATAAAACATTGAGTGT

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FIGURE 101

MAPHRPAPALLCALSLALCALSLPVRAATASRGASQAGAPQGRVPEARPNMSMVVEHPEFLKAGKEPGLQIWRVEK
FDLVPVPTNLYGDFFTGDAYVILKTVQLRNGNLQYDLHYWLGNNECSQDESGAAAIFTVQLDDYLNGRAVQHREVQ
GFESATFLGYFKSGLKVKKGVASGFKHVPNEVVQRLFQVKGRVV RATEVPVSWEFNNGDCFILDLGNNIH
QWCGSNSNRYERLKATQVSKGIRDNERSGRARVHVSEEGTEPEAMLQVLGPKPALPAGTEDTAKEDAANRKLAKL
YKVSNGAGTMSVSLVADENPFAQGALKSEDCFILDHGKDGFIFVWKQKQANTEERKAALKTASDFITKMDYPKQT
QVSVLPEGGETPLFKQFFKNWRDPDQTDLGLSYLSSIANVERVPFDAATLHTSTAMAAQHGMDDGTGQKQIW
RIEGSNKVPVDPATYQFYGGDSYIILYNYRHGGRQGQIITYNWQGAQSTQDEVAASAILTAQLDEELGGTPVQSR
VVQGKEPAHLMMSLFGGKPMIIYKGGSREGGQTAPASTRLFQVRANSAGATRAVEVLPKAGALNSNDAFVLKTPS
AAYLWVGTGASEAEKTGAQELLRVLRAQPVQVAEGSEPDGFWEALGGKAAYRTSPRLKDKMDAHPPLRFACSNK
IGRFVIEEVPGELMQEDLATDDVMLLDTWDQVFVWVGKDSQEEEKTEALTSAKRYIETDPANRDRRTPI TVVKQG
FEPPSFVGFGLGWDDYWSVDPLDRAMELAA

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FIGURE 102

GTTCCTCTCCCTGCCCGCACTCGCGAAGATCCGGAGGGACACCCGAGGCCCTGGGAGACCCCTGGGGAG
GTGAAAGTCAGAGAGCGAAGCGGGCGTGGCCCTAGGCCTGACCCCTCCCCCGGGGTAAGGCAGGGCACCCCGC
GAGCGCAGGGTCCCTACTGCTGATGGCACCCAGCTCTGGGCCAGACGCCGCTACCGTCCACCACCGGGTGC
TGGGTAAAATGTCGGTTCCAGGACCTTACAGCGGCCACTGGCCTCCTCAGCACCATCCGACCTCCATCCT
ATGAAGAGACAGTGGCTTTAACAGTTATTACCCACACCTCAGCTCCATGCCCTGGCCAACACTACGGGCTTG
TGACGGGCTGATGGGAAGGGCATGAATCCTCCTCGTATTATACCCAGCCAGCGCCATCCAAATAACAATC
CAATTACCGTGCAGACGGTCTACGTGCAGCACCCATCACCTTTGGACGCCATCCAAATGTGTTGCTT
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